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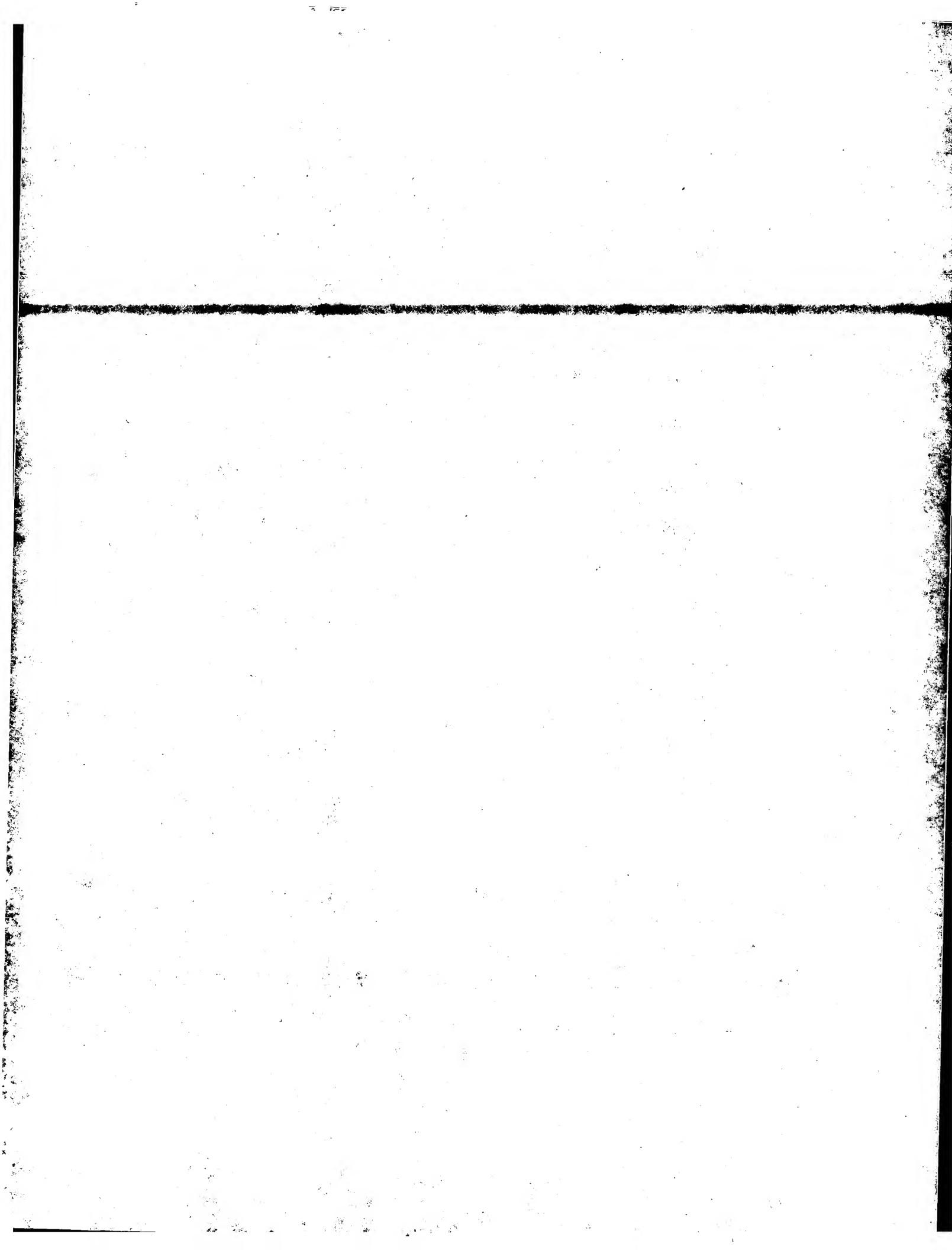
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(74) Agents: EISENSCHENK, Frank, C. et al.; Saliwanchik, Lloyd & Saliwanchik, 2421 N.W. 41st Street, Suite A-1, Gainesville, FL 32606-6669 (US).

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(71) Applicant (*for all designated States except US*): ARYx THERAPEUTICS [US/US]; Suite 1, 586 Weddell Drive, Sunnyvale, CA 94089 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): DRUZGALA, Pascal [FR/US]; 1512 Mission Boulevard, Santa Rosa, CA 95409 (US). MILNER, Peter, G. [GB/US]; 14690 Manuela Road, Los Altos Hills, CA 94022 (US). PFISTER, Jurg, R. [US/US]; 1500 Oak Avenue, Los Altos, CA 94024 (US).

A2

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(54) Title: MATERIALS AND METHODS FOR THE TREATMENT OF DIABETES, HYPERLIPIDEMIA, HYPERCHOLESTEROLEMIA, AND ATHEROSCLEROSIS

(57) Abstract: The subject invention provides pharmaceutical compounds useful in the treatment of Type II diabetes. These compounds are advantageous because they are readily metabolized by the metabolic drug detoxification systems. Particularly, thiazolidinedione analogs that have been designed to include esters within the structure of the compounds are provided. This invention is also drawn to methods of treating disorders, such as diabetes, comprising the administration of therapeutically effective compositions comprising compounds that have been designed to be metabolized by serum or intracellular hydrolases and esterases. Pharmaceutical compositions of the ester-containing thiazolidinedione analogs are also taught.

DESCRIPTIONMATERIALS AND METHODS FOR THE TREATMENT OF DIABETES,5 HYPERLIPIDEMIA, HYPERCHOLESTEROLEMIA, AND ATHEROSCLEROSISCross-Reference to Related Applications

This application claims priority to United States Provisional Applications
10 60/199,146, filed April 24, 2000 and 60/281,982, filed April 6, 2001, the disclosures
of which are each incorporated by reference in their entireties, including all figures,
tables, and chemical structures.

Background of the Invention

15

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct etiologies and pathogeneses. For example, diabetes mellitus is a disorder of carbohydrate metabolism,
20 characterized by hyperglycemia and glycosuria and resulting from inadequate production or utilization of insulin.

Noninsulin-dependent diabetes mellitus (NIDDM), often referred to as Type II diabetes, is a form of diabetes that occurs predominantly in adults who produce adequate levels of insulin but who have a defect in insulin-mediated utilization and
25 metabolism of glucose in peripheral tissues. Overt NIDDM is characterized by three major metabolic abnormalities: resistance to insulin-mediated glucose disposal, impairment of nutrient-stimulated insulin secretion, and overproduction of glucose by the liver. It has been shown that for some people with diabetes a genetic predisposition results from a mutation in the gene(s) coding for insulin and/or the insulin receptor and/or insulin-mediated signal transduction factor(s), thereby
30 resulting in ineffective insulin and/or insulin-mediated effects thus impairing the utilization or metabolism of glucose.

For people with Type II diabetes, insulin secretion is often enhanced, presumably to compensate for insulin resistance. Eventually, however, the B-cells

fail to maintain sufficient insulin secretion to compensate for the insulin resistance. Mechanisms responsible for the B-cell failure have not been identified, but may be related to the chronic demands placed on the B-cells by peripheral insulin resistance and/or to the effects of hyperglycemia. The B-cell failure could also occur as an 5 independent, inherent defect in "pre-diabetic" individuals.

NIDDM often develops from certain at risk populations. One such population is individuals with polycystic ovary syndrome (PCOS). PCOS is the most common endocrine disorder in women of reproductive age. This syndrome is characterized by hyperandrogenism and disordered gonadotropin secretion producing oligo- or 10 anovulation. Recent prevalence estimates suggest that 5-10% of women between 18-44 years of age (about 5 million women, according to the 1990 census) have the full-blown syndrome of hyperandrogenism, chronic anovulation, and polycystic ovaries. Despite more than 50 years since its original description, the etiology of the syndrome 15 remains unclear. The biochemical profile, ovarian morphology, and clinical features are non-specific; hence, the diagnosis remains one of exclusion of disorders, such as androgen-secreting tumors, Cushing's Syndrome, and late-onset congenital adrenal hyperplasia. PCOS is associated with profound insulin resistance resulting in substantial hyperinsulinemia. As a result of their insulin resistance, PCOS women are at increased risk to develop NIDDM.

20 NIDDM also develops from the at risk population of individuals with gestational diabetes mellitus (GDM). Pregnancy normally is associated with progressive resistance to insulin-mediated glucose disposal. In fact, insulin sensitivity is lower during late pregnancy than in nearly all other physiological conditions. The insulin resistance is thought to be mediated in large part by the effects of circulating 25 hormones such as placental lactogen, progesterone, and cortisol, all of which are elevated during pregnancy. In the face of the insulin resistance, pancreatic B-cell responsiveness to glucose normally increases nearly 3-fold by late pregnancy, a response that serves to minimize the effect of insulin resistance on circulating glucose levels. Thus, pregnancy provides a major "stress-test" of the capacity for B-cells to 30 compensate for insulin resistance.

Other populations thought to be at risk for developing NIDDM include persons with Syndrome X; persons with concomitant hyperinsulinemia; persons with insulin resistance characterized by hyperinsulinemia and by failure to respond to exogenous insulin; and persons with abnormal insulin and/or evidence of glucose

disorders associated with excess circulating glucocorticoids, growth hormone, catecholamines, glucagon, parathyroid hormone, and other insulin-resistant conditions.

Failure to treat NIDDM can result in mortality due to cardiovascular disease
5 and in other diabetic complications including retinopathy, nephropathy, and peripheral neuropathy. There is a substantial need for a method of treating at risk populations such as those with PCOS and GDM in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating
10 accompanying disorders of the populations at risk for NIDDM.

For many years, treatment of NIDDM has involved a program aimed at lowering blood sugar with a combination of diet and exercise. Alternatively, treatment of NIDDM can involve oral hypoglycemic agents, such as sulfonylureas alone or in combination with insulin injections. Recently, alpha-glucosidase inhibitors, such as a
15 carboys, have been shown to be effective in reducing the postprandial rise in blood glucose (Lefevre, et al., Drugs 1992; 44:29-38). In Europe and Canada another treatment used primarily in obese diabetics is metformin, a biguanide.

Compounds useful in the treatment of the various disorders discussed above, and methods of making the compounds, are known and some of these are disclosed in
20 U.S. Pat. Nos. 5,223,522 issued Jun. 29, 1993; 5,132,317 issued Jul. 12, 1992; 5,120,754 issued Jun. 9, 1992; 5,061,717 issued Oct. 29, 1991; 4,897,405 issued Jan.
30, 1990; 4,873,255 issued Oct. 10, 1989; 4,687,777 issued Aug. 18, 1987; 4,572,912 issued Feb. 25, 1986; 4,287,200 issued Sep. 1, 1981; 5,002,953, issued Mar. 26, 1991;
U.S. Pat. Nos. 4,340,605; 4,438,141; 4,444,779; 4,461,902; 4,703,052; 4,725,610;
25 4,897,393; 4,918,091; 4,948,900; 5,194,443; 5,232,925; and 5,260,445; WO
91/07107; WO 92/02520; WO 94/01433; WO 89/08651; and JP Kokai 69383/92. The
compounds disclosed in these issued patents and applications are useful as therapeutic
agents for the treatment of diabetes, hyperglycemia, hypercholesterolemia, and
hyperlipidemia. The teachings of these issued patents are incorporated herein by
30 reference in their entireties.

Drug toxicity is an important consideration in the treatment of humans and animals. Toxic side effects resulting from the administration of drugs include a variety of conditions that range from low-grade fever to death. Drug therapy is justified only when the benefits of the treatment protocol outweigh the potential risks

associated with the treatment. The factors balanced by the practitioner include the qualitative and quantitative impact of the drug to be used as well as the resulting outcome if the drug is not provided to the individual. Other factors considered include the physical condition of the patient, the disease stage and its history of progression, and any known adverse effects associated with a drug.

Drug elimination is typically the result of metabolic activity upon the drug and the subsequent excretion of the drug from the body. Metabolic activity can take place within the vascular supply and/or within cellular compartments or organs. The liver is a principal site of drug metabolism. The metabolic process can be categorized into synthetic and nonsynthetic reactions. In nonsynthetic reactions, the drug is chemically altered by oxidation, reduction, hydrolysis, or any combination of the aforementioned processes. These processes are collectively referred to as Phase I reactions.

In Phase II reactions, also known as synthetic reactions or conjugations, the parent drug, or intermediate metabolites thereof, are combined with endogenous substrates to yield an addition or conjugation product. Metabolites formed in synthetic reactions are, typically, more polar and biologically inactive. As a result, these metabolites are more easily excreted via the kidneys (in urine) or the liver (in bile). Synthetic reactions include glucuronidation, amino acid conjugation, acetylation, sulfoconjugation, and methylation.

One of the drugs used to treat Type II diabetes is troglitazone. The major side effects of troglitazone are nausea, peripheral edema, and abnormal liver function. Other reported adverse events include dyspnea, headache, thirst, gastrointestinal distress, insomnia, dizziness, incoordination, confusion, fatigue, pruritus, rash, alterations in blood cell counts, changes in serum lipids, acute renal insufficiency, and dryness of the mouth. Additional symptoms that have been reported, for which the relationship to troglitazone is unknown, include palpitations, sensations of hot and cold, swelling of body parts, skin eruption, stroke, and hyperglycemia. Accordingly, forms of glitazones which have fewer, or no, adverse effects (i.e., less toxicity) are desirable.

The principal difference between the compounds of the present invention and related compounds is the presence of a carboxyl group, either OOC- or COO-, directly attached to the 4-position of the phenyl ring. In the literature,

thiazolidinediones having similar therapeutic properties have an ether function at the 4-position of the phenyl ring instead of a carboxyl group.

The presence of the carboxyl group has significant consequences for the biological behavior of these new compounds. The present compounds are primarily 5 metabolized by hydrolytic enzymatic systems, whereas compounds having an ether function are metabolized only by oxidative enzymes. Hydrolytic enzymatic systems are ubiquitous, non-oxidative, not easily saturable, and non-inducible, and, therefore, reliable. By contrast, oxidative systems are mediated by the P-450 isozymes. These 10 systems are localized, mainly, in the liver, saturable and inducible (even at low concentrations of therapeutic compounds) and therefore are highly unreliable.

The compounds of the subject invention do not rely on saturable hepatic systems for their metabolism and elimination, whereas the prior art compounds exert a heavy bio-burden on hepatic functions, especially in the presence of other drugs that rely on similar enzymes for detoxification. Thus, the present compounds have a much 15 more desirable toxicity profile than prior art compounds, especially when considering liver toxicity and potentially fatal drug-drug interactions.

Upon metabolism by plasma and tissue esterases, the compounds of this invention are hydrolyzed into 2 types of molecules: 1) an alcohol or a phenol, and 2) a carboxylic acid. Therefore, any compound that yields compound 1, compound 2, 20 compound 3, or compound 4, as defined in Table I, as a primary metabolite falls under the definition of this invention. This concept is illustrated in Figure 1, taking compound 9 (of Table I) and compound 145 (of Table X) as specific examples of compounds giving 1 and 3, respectively, upon non-oxidative metabolism by esterases.

25

Brief Summary of the Invention

The subject invention provides materials and methods for the safe and effective treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis. In a preferred embodiment, the subject invention provides therapeutic 30 compounds for the treatment of diabetes. The compounds of the subject invention can be used to treat at-risk populations, such as those with PCOS and GDM, in order to prevent or delay the onset of NIDDM thereby bringing relief of symptoms, improving the quality of life, preventing acute and long-term complications, reducing mortality and treating accompanying disorders.

Advantageously, the subject invention provides compounds that are readily metabolized by the physiological metabolic drug detoxification systems. Specifically, in a preferred embodiment, the therapeutic compounds of the subject invention contain an ester group, which does not detract from the ability of these compounds to 5 provide a therapeutic benefit, but which makes these compounds more susceptible to degradation by hydrolases, particularly serum and/or cytosolic esterases. The subject invention further provides methods of treatment comprising the administration of these compounds to individuals in need of treatment for Type II diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis.

10 In a further embodiment, the subject invention pertains to the breakdown products that are formed when the therapeutic compounds of the subject invention are acted upon by esterases. These breakdown products can be used as described herein to monitor the clearance of the therapeutic compounds from a patient.

15 In yet a further embodiment, the subject invention provides methods for synthesizing the therapeutic compounds of the subject invention.

Brief Description of the Figures

Figure 1 depicts exemplary metabolic breakdown products resulting from the 20 actions of esterases on compounds of the invention.

Figures 2-3 provide an exemplary synthetic scheme for compounds 1 through 4 (of Table I). These compounds can be conveniently prepared by the Knoevenagel reaction between an aldehyde and thiazolidine-2,4-dione using, for example, sodium 25 acetate in acetic anhydride, or piperidine and benzoic acid in methylene chloride as a reaction medium.

Figure 4 illustrates an alternative reaction scheme for the production of compound 1 (of Table I). In this reaction scheme, *para*-anisidine undergoes a diazotation reaction with sodium nitrite and hydrochloric acid. The diazonium 30 chloride salt undergoing, in turn, a radical reaction with methyl acrylate and then a cyclization reaction with thiourea, the product of which is hydrolyzed to the thiazolidinedione molecule.

Figure 5 shows an exemplary synthetic scheme for the compounds described in Table I (compounds 5 to 32). These compounds can be made via an esterification reaction between **1** or **2** and an appropriately substituted carboxylic acid, or between **3** or **4** and an appropriately substituted alcohol.

5

Figure 6 depicts the synthesis of the 4-oxazoleacetic acid and the 4-oxazoleethanol moiety starting from aspartic acid derivatives in which R₂ and R₃ are methyl or hydrogen.

10

Figure 7 describes the synthesis of the 4-oxazolecarboxylic acid and 4-oxazolemethanol groups. The synthesis starts from ethyl acetoacetate in which a 2-amino-group is introduced via oxime formation followed by reduction with zinc powder. The synthesis then proceeds as before, where the R₁ group is introduced by acylating the amino group, followed by cyclization with sulfuric acid in ethyl acetate, 15 and finally ester cleavage or reduction to the alcohol.

Figure 8 shows how steric hindrance can be introduced under the form of methyl groups on the 4-methanol moiety. Starting from pentane-2,4-dione and following the same synthetic sequence as in Figure 7 leads to the 4-acetyloxazole 20 compounds which can be reduced by sodium borohydride to the 4-(1-ethyl)oxazole, or which can be transformed to 4-(2-hydroxy-2-propyl) oxazole with a methyl Grignard reagent such as methyl magnesium iodide.

Figure 9 illustrates an alternative synthetic scheme wherein condensation of a thioamide with methyl 4-bromo-3-oxopentanoate gives methyl 4-thiazoleacetate. Ester cleavage with lithium hydroxide or reduction with lithium aluminum hydride gives the corresponding acid or the alcohol, respectively.

Figures 10-17 depict the synthesis of compounds **105** to **224** in Tables VI to 30 XVII. These compounds contain an amino acid or an amino alcohol as part of their structure.

Figure 18 provides an exemplary synthetic pathway for compounds **225** to **242** (Table XVIII). These compounds are oxazoline-4-carboxylic acid types of

compounds. Their synthesis (Figure 18) starts from serine ($R_5=H$) or from threonine ($R_5=CH_3$) benzyl ester. The ester is coupled with an alkyl or an arylcarboxylic acid using for example EDC as a coupling agent. The serine or threonine group then cyclizes into an oxazoline upon treatment with thionyl chloride. Coupling with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione using DCC/DMAP/methylene chloride gives compounds 225 to 242.

Figures 19-20 illustrate the activity of representative compounds on serum glucose and insulin levels in non-insulin dependent diabetic mellitus (NIDDM) KK-^A male mice. Post-treatment data for each group were transferred to a percentage of pretreatment values and unpaired Student's t test was used for comparison between vehicle and test substance treated groups. Results show a significant reduction of both serum glucose and serum insulin relative to the vehicle control group. Reduction in serum glucose and serum insulin levels were comparable to the reduction observed in the troglitazone-treated animals. The results are also presented in Table XXI.

Brief Description of the Tables

Tables I-XXII depict exemplary compounds according to the invention. The term "db" indicates a double bond between P and Q.

Table XXIII illustrates the effects of exemplary compounds on serum glucose and insulin levels in NIDDM mice.

Detailed Disclosure of the Invention

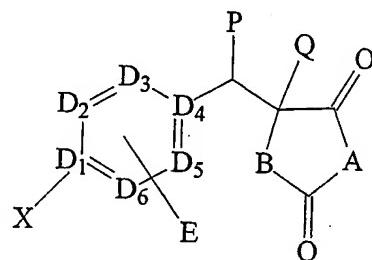
The subject invention provides materials and methods for the treatment of non-insulin dependent diabetes mellitus (NIDDM), hyperlipidemia, hypercholesterolemia, and atherosclerosis. Advantageously, the therapeutic compounds of the subject invention are stable in storage but have a shorter half-life in the physiological environment than other drugs which are available for treatment of diabetes; therefore, the compounds of the subject invention can be used with a lower incidence of side effects and toxicity, especially in patients having elevated liver function or compromised liver function.

In a preferred embodiment of the subject invention, therapeutic compounds are provided which are useful in the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and atherosclerosis and which contain an ester group which is acted upon by esterases thereby breaking down the compound and facilitating its efficient removal from the treated individual. In a preferred embodiment the therapeutic compounds are metabolized by the Phase I drug detoxification system and are exemplified by the compound of Formula I.

The compounds of Formula I can be generally described as 5-benzyl- or 5-benzylidene-thiazolidine-2,4-dione compounds having a carboxyl group directly attached to the *para*-position of the phenyl ring. These compounds represent a new class of chemical compounds having therapeutic properties for the treatment of type-II diabetes mellitus, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

15

Formula I



20

For compounds of Formula I:

A and B may be the same or different and are C, N, NO, NH, SO₀₋₂, O;
D₁-D₆ can be the same or different and are C, N, S, or O;
E can be attached to one or more of the atoms located at D₁-D₆;
P and Q can be a double bond; or
P, Q, and E can be the same or different and are a moiety selected from the group consisting of H, C₁₋₁₀ alkyl, substituted alkyl groups, substituted or unsubstituted carboxylic acids, substituted or unsubstituted carboxylic esters, halogen, carboxyl, hydroxyl, phosphate, phosphonate, aryl, CN, OH, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄.

Exemplary heterocyclic groups include, but not limited to, morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine or thiadiazoline.

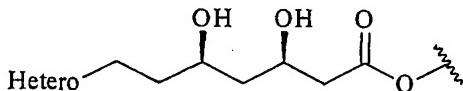
Substituted carboxylic acids, substituted carboxylic esters, and substituted alkyl groups can be substituted at any available position with a moiety selected from the group consisting of C₁₋₁₀ alkyl, halogen, CN, OH, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄. Exemplary heterocyclic groups include, but are not limited to, morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine, and thiadiazoline.

X is -OH, -COOH, or a substituted carboxylic group having the carboxyl moiety OOC- or COO- directly attached to the phenyl ring of the compound of Formula 1. The carboxylic acid group can be substituted with a moiety selected from the group consisting of alkyloxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, arylcarbonyloxy, heteroalkyloxycarbonyl, heteroalkylcarbonyloxy, heteroaryl-oxycarbonyl, and heteroarylcarbonyloxy, each of which is, optionally, substituted with C₁₋₁₀ alkyl, CN, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄. In other embodiments, the substituted carboxylic group can be substituted with a moiety selected from the group consisting of C₁₋₁₀ alkyl, CN, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄. Exemplary heterocyclic groups include, but are not limited to, morpholine, triazole, imidazole, pyrrolidine,

piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine, and thiadiazoline.

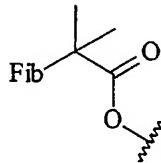
In specific embodiments, X can be hydroxyl, hydroxycarbonyl, 1-methyl-1-cyclohexylcarbonyloxy, 1-methyl-1-cyclohexylmethoxycarbonyl, 5-ethyl-2-pyridyl-5-acetoxy, 5-ethyl-2-pyridylmethoxy-carbonyl, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetra-methylchroman-2-ylmethoxy -carbonyl, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-penta-methyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl -2,3-dihydrobenzofuran-3-methoxycarbonyl, 2-hydroxybenzoyloxy, or 2,4-dihydroxybenzoyloxy.

In other embodiments, X can be



wherein Hetero is an aromatic, cyclic, or alicyclic moiety that can contain heteroatoms. In certain specific embodiments, Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms that are generally part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl, a component of lovastatin.

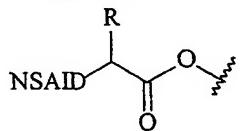
Alternatively, X can be



wherein Fib is an aromatic, cyclic, or alicyclic moiety that can contain heteroatoms. In certain specific embodiments, Fib moieties are part of the fibrate-family of lipid lowering agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a

component of clofibrate acid, and 3-(2,5-xylyloxy)-1-propyl, a component of gemfibrozil.

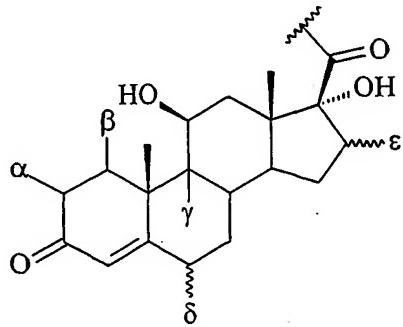
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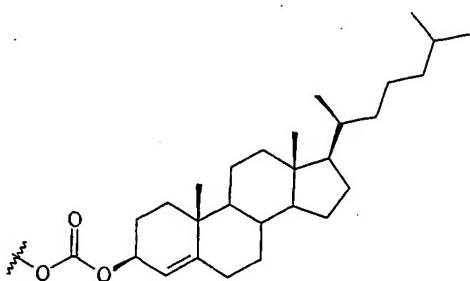
wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 10 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl.

In another embodiment, X can be

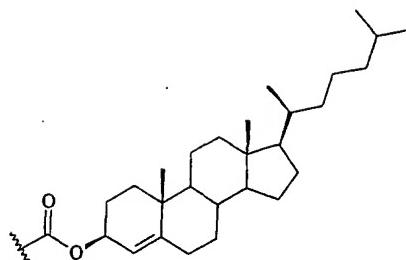


where α and β are hydrogen or α and β form a bond, and where γ , δ , and ϵ , are 15 independently hydrogen, hydroxy, fluoro, chloro, or methyl.

Alternatively, X can be



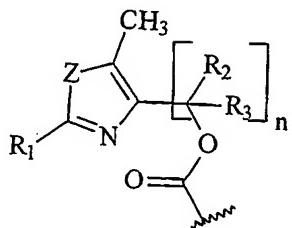
or



5

X can also be of the general formula

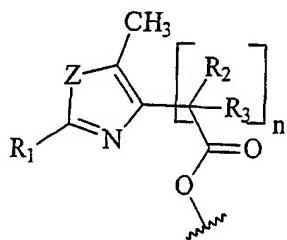
10



In such embodiments, n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 15 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

Other embodiments provide compounds wherein X is

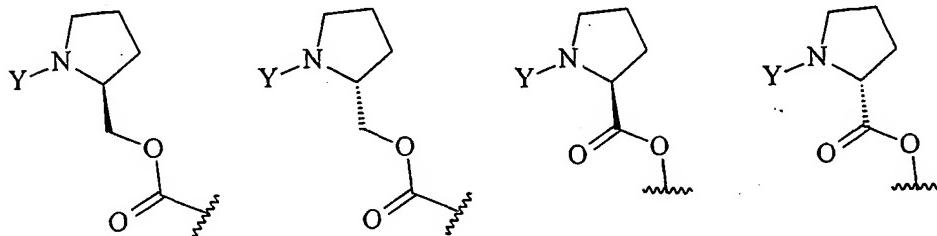
20



in which n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples

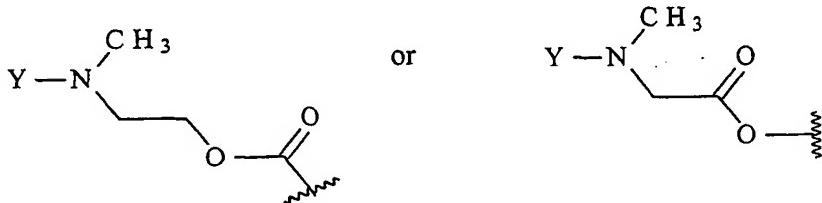
include compounds where R1 is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

In other embodiments, X is a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas



in which Y is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazolinyl, 5-methyl-2-thiazolinyl, 4,5-dimethyl-2-oxazolinyl, 4,5-dimethyl-2-thiazolinyl, 5-phenyl-2-thiazolinyl, 2-thiazolinyl, 4-methyl-5-phenyl-2-thiazolinyl, 5-methyl-4-phenyl-2-thiazolinyl, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-pyridinyl, 6-methoxy-2-pyridinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

Alternatively X is an N-substituted 2-methylaminoethoxycarbonyl or a N-substituted 2-methylaminoacetoxy, having the following formulas:



in which Y is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetra-

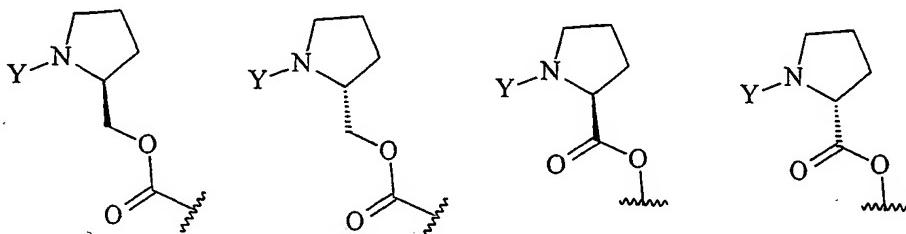
5 methylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-

10 methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazolinyl, 5-methyl-2-thiazolinyl, 4,5-dimethyl-2-oxazolinyl, 4,5-dimethyl-2-thiazolinyl, 5-phenyl-2-thiazolinyl, 2-thiazolinyl, 4-methyl-5-phenyl-2-thiazolinyl, 5-methyl-4-phenyl-2-thiazolinyl, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-pyridinyl, 6-methoxy-2-pyridinyl, 2-

15 hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

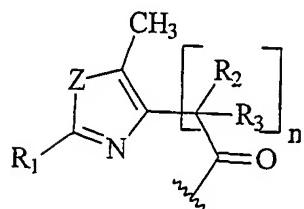
X can also be a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas:

20



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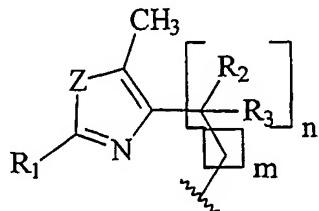
wherein Y is



n is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-

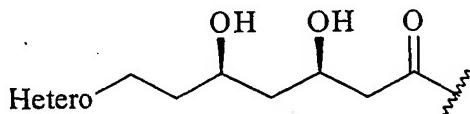
5 pyrazinyl; or

Y is



n is 0 or 1; m is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples 10 include compounds where R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl; or

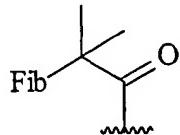
Y is



15

wherein Hetero is an aromatic, cyclic, or alicyclic moiety that usually contains heteroatoms. In certain specific embodiments, these moieties are part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-20 -1-(1H-pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl, a component of lovastatin; or

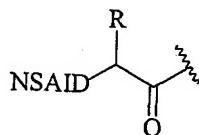
Y is



25 wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms. In some embodiments, these moieties are part of the fibrate-family of lipid lowering

agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a component of clofibrate acid, and 3-(2,5-xylyloxy)-1-propyl, a component of gemfibrozil; or

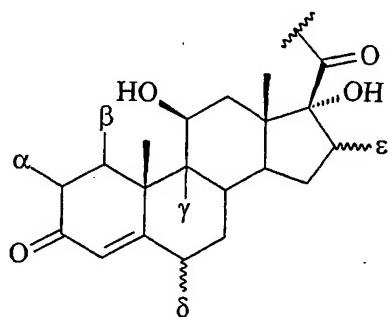
5 Y is



wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the

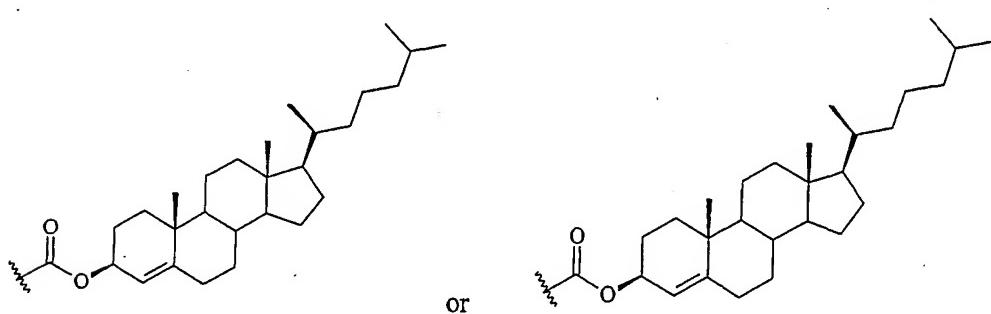
10 family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl or

Y can be

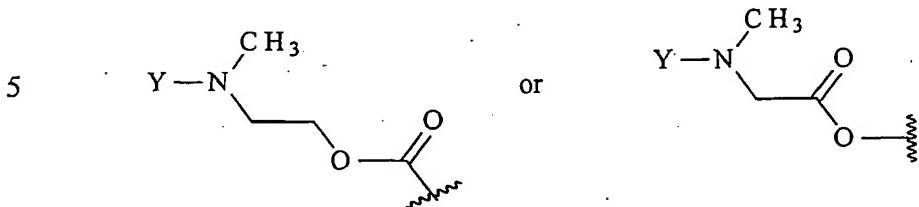


15 where α and β are hydrogen or α and β form a bond, and where γ , δ , and ϵ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

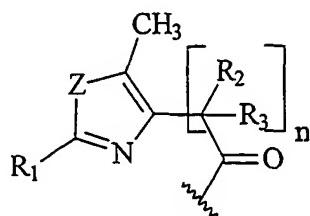
Y can be



Alternatively X can be an N-substituted 2-methylaminoethoxycarbonyl or an N-substituted 2-methylaminoacetoxy, having the following formulas:

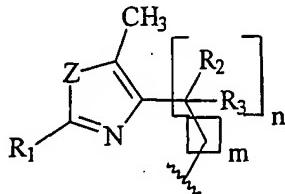


10 wherein Y is



n is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl; or

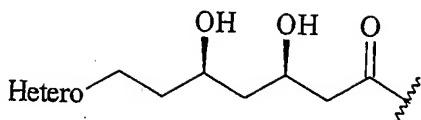
Y is



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n is 0 or 1; m is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl; or

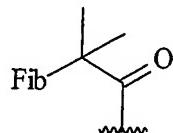
Y is



wherein Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms.

- 5 In certain specific embodiments, these moieties are part of the structure of the statin-family of lipid lowering agents. Preferred examples include, but are not limited to, 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl, a component of atorvastatin, and 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyloxy)-3,7-dimethyl-8-naphthalenyl, a component of lovastatin; or

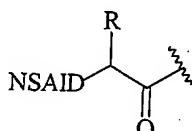
10 Y is



wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms. In some embodiments, these moieties are part of the fibrate-family of lipid lowering

- 15 agents. Preferred examples include, but are not limited to 4-(4-chlorobenzoyl)phenoxy, a component of fenofibric acid, 4-chlorophenoxy, a component of clofibrate acid, and 3-(2,5-xylyloxy)-1-propyl, a component of gemfibrozil; or

Y is

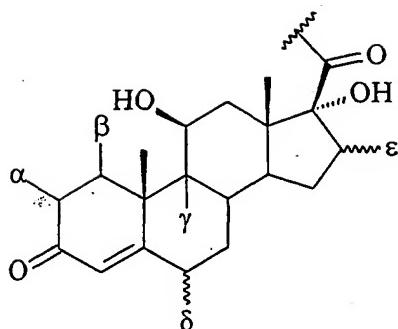


20

wherein R is hydrogen or methyl, and in which NSAID means an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms and that are generally part of the family of non-steroidal anti-inflammatory agents. Preferred examples include, but are not limited to 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 25 6'-methoxy-2'-naphthyl, and 6'-methoxy-2'-naphthylmethyl; or

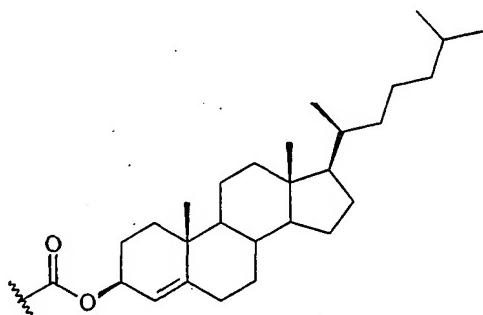
Y can be

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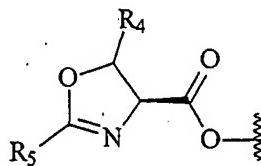
where α and β are hydrogen or α and β form a bond, and where γ , δ , and ϵ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

Y can be



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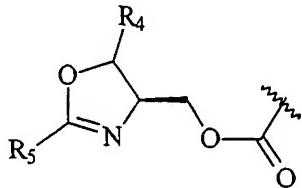
Other embodiments provide compounds wherein X is



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R₄ is hydrogen or methyl, and where R₅ is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R₅ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

X can also be



20

wherein R4 is hydrogen or methyl, and where R5 is aryl or heteroaryl, alkyl or heteroalkyl. Preferred non-limiting examples include compounds where R5 is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-
5 methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

In one embodiment, A is NH; B is sulfur (S); P and Q are a double bond or
10 hydrogen (H); E is hydrogen (H) and is attached to each of D₁ through D₆; D₁ through
D₆ are carbon (C); and X can be any of the structures provided *supra*.

Modifications of the compounds disclosed herein can readily be made by
those skilled in the art. Thus, analogs, derivatives, and salts of the exemplified
compounds are within the scope of the subject invention. With a knowledge of the
15 compounds of the subject invention, and their structures, skilled chemists can use
known procedures to synthesize these compounds from available substrates.

As used in this application, the terms "analog" and "derivatives" refer to
compounds which are substantially the same as another compound but which may
have been modified by, for example, adding additional side groups. The terms
20 "analog" and "derivatives" as used in this application also may refer to compounds
which are substantially the same as another compound but which have atomic or
molecular substitutions at certain locations in the compound.

Analogs or derivatives of the exemplified compounds can be readily prepared
using commonly known, standard reactions. These standard reactions include, but are
25 not limited to, hydrogenation, methylation, acetylation, and acidification reactions.
For example, new salts within the scope of the invention can be made by adding
mineral acids, e.g., HCl, H₂SO₄, etc., or strong organic acids, e.g., formic, oxalic, etc.,
in appropriate amounts to form the acid addition salt of the parent compound or its
derivative. Also, synthesis type reactions may be used pursuant to known procedures
30 to add or modify various groups in the exemplified compounds to produce other
compounds within the scope of the invention.

The subject invention further provides methods of treating disorders, such as
diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia, comprising the
administration of a therapeutically effective amount of esterified thiazolidinedione

analogs to an individual in need of treatment. Thiazolidinedione based compounds include troglitazone (for example, REZULIN), pioglitazone, and rosiglitazone. Accordingly, the subject invention provides esterified thiazolidinedione analogs and pharmaceutical compositions of these esterified compounds. The compounds and 5 compositions according to the invention can also be administered in conjunction with other therapeutic compounds, therapeutic regimens, compositions, and agents suitable for the treatment of disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia. Thus, the invention includes combination therapies wherein the compounds and compositions of the invention are used in conjunction with other 10 therapeutic agents for the treatment of disorders, such as diabetes, atherosclerosis, hypercholesterolemia, and hyperlipidemia.

The compounds of this invention have therapeutic properties similar to those of the unmodified parent compounds. Accordingly, dosage rates and routes of administration of the disclosed compounds are similar to those already used in the art 15 and known to the skilled artisan (see, for example, *Physicians' Desk Reference*, 54th Ed., Medical Economics Company, Montvale, NJ, 2000).

The compounds of the subject invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in detail in a number of sources that are well known and readily 20 available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulations that can be used in connection with the subject invention. In general, the compositions of the subject invention are formulated such that an effective amount of the bioactive compound(s) is combined with a suitable carrier in order to facilitate effective administration of the 25 composition.

In accordance with the subject invention, pharmaceutical compositions are provided which comprise, as an active ingredient, an effective amount of one or more of the compounds of the invention and one or more non-toxic, pharmaceutically acceptable carriers or diluents. Examples of such carriers for use in the invention 30 include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, and equivalent carriers and diluents. Additional therapeutic agents suitable for the treatment of disorders such as diabetes, atherosclerosis, hypercholesterolemia, and hyper-lipidemia can also be incorporated into pharmaceutical agents according to the invention.

Further, acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances that may act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, 5 preservatives, tablet disintegrating agents or encapsulating materials.

The disclosed pharmaceutical compositions may be subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, such as packeted tablets, capsules, and powders in paper or plastic containers or in vials or ampoules. Also, the unit dosage can be a liquid based 10 preparation or formulated to be incorporated into solid food products, chewing gum, or lozenge.

Compounds 1 through 4 (of Table I) can be conveniently prepared by the Knoevenagel reaction between an aldehyde and thiazolidine-2,4-dione, using for example sodium acetate in acetic anhydride, or piperidine and benzoic acid in 15 methylene chloride as a reaction medium. This is illustrated in Figure 2 and Figure 3. Alternatively, compound 1 can be prepared by the method described in Figure 4. In this reaction scheme, *para*-anisidine undergoes a diazotation reaction with sodium nitrite and hydrochloric acid. The diazonium chloride salt undergoing, in turn, a radical reaction with methyl acrylate and then a cyclization reaction with thiourea, 20 the product of which is hydrolyzed to the thiazolidinedione molecule.

The compounds described in Table I (compounds 5 to 32) can all be made via an esterification reaction between 1 or 2 and an appropriately substituted carboxylic acid, or between 3 or 4 and an appropriately substituted alcohol. The esterification reaction can be facilitated by the presence of a catalyst in the reaction medium, such 25 as a small amount of concentrated sulfuric acid for example. Preferably, especially if the alpha-position to the carbonyl is an asymmetric center, an activated functional derivative of the carboxylic acid is made. Numerous functional derivatives of carboxylic acids used in esterification reactions have been described in the scientific literature. The most commonly used activated functional derivatives are acyl 30 chlorides, anhydrides and mixed anhydrides, and activated esters. In one aspect of this invention dicyclohexyl carbodiimide (DCC) was used as an activating agent (Figure 5).

Compounds 33 to 104 are functionalized 5-methyloxazole and functionalized 5-methylthiazole derivatives. They all have various functional groups attached to the

2-position (R_1 in Tables II to V), and at the 4-position, which is the enzymatically labile link with the thiazolidine portion of the molecule. The enzymatically labile link is either an ester (COO^-) or a reverse ester (OOC^-) and can be substituted with 0, 1, or 2 methyl groups at the alpha-position from the oxazole or thiazole ring (R_2 and R_3 in 5 Tables II to V).

The synthesis of compounds 33 to 104 is described in general terms in Figures 7-10. Figure 6 describes the synthesis of the 4-oxazoleacetic acid and the 4-oxazoleethanol moiety starting from aspartic acid derivatives in which R_2 and R_3 are methyl or hydrogen. In a typical example, γ -benzyl aspartate is acetylated and then 10 decarboxylated to benzyl 3-acetamido-4-oxovalerate using acetic anhydride as an acetylating agent followed by potassium hydroxide in order to obtain the decarboxylated product. This in turn is transformed into methyl 3-amino-4-oxovalerate using standard hydrolytic and esterification procedures, for example refluxing in dilute hydrochloric acid followed by reaction in thionyl chloride and 15 methanol. The R_1 group is then introduced by acylating the 3-amino group using the appropriate acyl or aroyl chloride. There is almost no limitation to the nature of the R_1 group being introduced at this stage, as shown in Tables II to V where various R_1 groups are described. Cyclization to an oxazole ring is then effected using sulfuric acid as a catalyst in ethyl acetate as a solvent. At this stage, ester hydrolysis using 20 lithium hydroxide in methanol gives the desired 4-oxazoleacetic acid derivatives, whereas reduction of the ester with lithium aluminum hydride or reduction of the acid using diborane gives the 4-oxazoleethanol analogs.

Figure 7 describes the synthesis of the 4-oxazolecarboxylic acid and 4-oxazolemethanol groups. The synthesis starts from ethyl acetoacetate in which a 2-amino-group is introduced via oxime formation followed by reduction with zinc powder. The synthesis then proceeds as before, where the R_1 group is introduced by acylating the amino group, followed by cyclization with sulfuric acid in ethyl acetate, and finally ester cleavage or reduction to the alcohol.

Figure 8 shows how steric hindrance can be introduced under the form of 30 methyl groups on the 4-methanol moiety. Starting from pentane-2,4-dione, following the same synthetic sequence as in Figure 7 leads to the 4-acetyloxazole compounds which can be reduced by sodium borohydride to the 4-(1-ethyl)oxazole. Alternatively, the compounds can be transformed by methylmagnesium iodide into

the tertiary alcohol analogs. In another embodiment, condensation of a thioamide with methyl 4-bromo-3-oxopentanoate gives methyl 4-thiazoleacetate, as described in Figure 9. Ester cleavage with lithium hydroxide or reduction with lithium aluminum hydride gives the corresponding acid or the alcohol, respectively.

5 Compounds 105 to 224 in Tables VI to XVII all have an amino acid or an amino alcohol as part of their structure. Their synthesis is described in Figures 10 to 18. Any amino acid can be used in the synthesis of compounds according to this aspect of the invention. In certain embodiments, the amino acid group can be either proline or N-methyl glycine and the amino alcohol group is their alcohol equivalent,
10 *i.e.*, prolinol or N-methyl glycinol, respectively. As shown in Figures 10 to 13, the reaction of an alkyl chloride or a 2-heteroaryl chloride with proline, prolinol, N-methyl glycine, or N-methyl glycinol, in THF and triethylamine gives the corresponding N-alkyl or N-heteroaryl adduct, respectively. When these adducts are carboxylic acids, such as in Figures 10 and 12, they react with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione in the presence of DCC and DMAP to give
15 compounds 105-108, 111, 112, 125-128, 131, 132, 185-188, 191, 192. Carboxylic acid adducts react with 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds 115-118, 121, 122, 135-138, 141, 142, 195-198, 201, 202. When these adducts are alcohols, such as in Figures 11 and
20 13, they react with 5-(4-carboxybenzyl)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds 145-148, 151, 152, 165-168, 171, 172, 205-208, 211, 212. Alcohol adducts react with 5-(4-carboxybenzylidene)thiazolidine-2,4-dione in the presence of DCC and DMAP to give compounds 155-158, 161, 162, 175-178, 181, 182, 215-218, 221, 222.

25 Alternatively, the amino acid or amino alcohol group can be linked to another group via an amide function, such as described in Figures 14 to 17. The synthesis of such compounds is straightforward. When the compounds contain an amino acid, as in Figures 14 and 16, the synthetic sequence is an amide bond formation, ester deprotection, and ester formation.

30 As an illustrative example, (R)-Trolox[®] is combined with L-proline methyl ester, in the presence of DCC and DMAP in methylene chloride to form an amide intermediate. The methyl ester of the proline group is then cleaved with lithium hydroxide in methanol, and the resulting carboxylic acid is combined with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione in DCC/DMAP/methylene chloride to give

compound 109. The (S)-isomer, compound 110, is made in a similar way. The same kind of synthetic scheme leads to compounds 113, 114, 119, 120, 123, 124, 129, 130, 133, 134, 139, 140, 143, 144, 189, 190, 193, 194, 199, 200, 203, and 204.

When the compounds contain an amino alcohol, as in Figures 15 and 17, the synthetic sequence is an amide bond formation, followed by an ester bond formation. As an illustrative example, (R)-Trolox® is combined with L-prolinol in the presence of DCC and DMAP in methylene chloride to form an amide intermediate. The resulting amide is combined with 5-(4-carboxybenzyl)thiazolidine-2,4-dione in DCC/DMAP/methylene chloride to give compound 149. The (S)-isomer, compound 150, is made in a similar way. The same kind of synthetic scheme leads to compounds 153, 154, 159, 160, 163, 164, 169, 170, 173, 174, 179, 180, 183, 184, 209, 210, 213, 214, 219, 220, 223, and 224.

Compounds 225 to 242 (Table XVIII) are oxazoline-4-carboxylic acid types of compounds. Their synthesis (Figure 18) starts from serine ($R_5=H$) or from threonine ($R_5=CH_3$) benzyl ester. The ester is coupled with an alkyl or an arylcarboxylic acid using for example EDC as a coupling agent. The serine or threonine group then cyclizes into an oxazoline upon treatment with thionyl chloride. Coupling with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione using DCC/DMAP/methylene chloride gives compounds 225 to 242.

Compounds 243 to 248 (Table XIX) are thiazolidinedione molecules where X is a group containing a substituted 2-methyl-2-propionyl residue. Examples include the 2-methyl-2-(4-chlorophenoxy)propionyl moiety (clofibryl moiety), the 2-methyl-2-[4-(4-chlorobenzoyl)phenoxy]propionyl moiety (fenofibryl moiety), and 2,2-dimethyl-5-(2,5-xylyloxy)valeryl moiety (gemfibrozil moiety).

Compounds 249 to 252 (Table XX) are thiazolidinedione molecules where X is a group containing a substituted (R,R)-3,5-dihydroxyheptanoyl residue. Examples include the (βR , δR)-2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenyl-amino)carbonyl] 1H-pyrrole-1-(β, δ -dihydroxy)heptanoyl group (atorvastatin), and the 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethylnaphthalenyl-8-[(3R,5R)-7-heptanoyl group (lovastatin). The synthesis of these compounds proceeds as in the examples of Table I, (i.e., by a simple esterification procedure between the lipid-lowering agent and compound 1 or compound 2).

Compounds 253 to 260 (Table XXI) are thiazolidinedione molecules where X is a group containing an arylacetic acid residue, such as in molecules that have non-steroidal anti-inflammatory properties. In these examples, the X group is an ibuprofen, ibufenac, naproxen, diclofenac, or nabumetone residue. The synthesis of 5 these compounds is a simple ester formation reaction between the X group and compound 1 (P and Q are hydrogen) or compound 2 (P and Q form a bond).

Compounds 261 to 268 (Table XXII) are thiazolidinedione molecules where X is a group containing a cortienic acid residue, such as in molecules that have glucocorticoid anti-inflammatory properties. In these examples, the X group is a 10 cortienic acid, 1,2-dihydrocortienic acid, 6 α , 9 α -difluoro-1,2-dihydrocortienic acid, and a 9 α -fluoro-16 α -methyl-1,2-dihydrocortienic acid residue. The synthesis of these 15 compounds is a simple ester formation reaction between the X group and compound 1 (P and Q are hydrogen) or compound 2 (P and Q form a bond). Cortienic acid, one of the many metabolites of hydrocortisone in man, can be synthetized from 20 hydrocortisone by oxidation with sodium periodate. The substituted cortienic acid analogs can be made in an identical manner from the corresponding substituted glucocorticoids. This oxidation procedure is described in detail in [Druzgala P.: Novel Soft Anti-inflammatory Glucocorticoids for Topical Application. Ph.D. Dissertation (1985), University of Florida, Gainesville, FL, hereby incorporated by reference in its entirety].

Representative compounds were chosen and evaluated for activity on serum glucose and insulin levels in non-insulin dependent diabetic mellitus (NIDDM) KK-A y male mice. Post-treatment data for each group were transferred to a percentage of pretreatment values and unpaired Student's t test was used for comparison between 25 vehicle and test substance treated groups. Results show a significant reduction of both serum glucose and serum insulin relative to the vehicle control group. Reduction in serum glucose and serum insulin levels were comparable to the reduction observed in the troglitazone-treated animals. The results are presented in Table XXI and in Figures 19 and 20.

EXAMPLES

Example 1- To (S)-2-pyrrolidinemethanol (3.96g) in THF (30ml) is added 2-chlorobenzoxazole (5.90g) also in THF (80ml) and then, dropwise, triethylamine 5 (3.96g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid. Evaporate the solvent and dissolve the crude product in 5ml of methylene chloride. Pass through a silica plug (50g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been collected. The yield of (S)-1-(2-benzoxazolyl)-2-hydroxymethylpyrrolidine is 8.2g.

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Example 2-To (S)-2-pyrrolidinemethanol (3.96g) in THF (30ml) is added 2-chlorobenzothiazole (6.50g) also in THF (80ml) and then, dropwise, triethylamine (3.96g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid. Evaporate the solvent and dissolve the crude product in 5ml of methylene chloride. 15 Pass through a silica plug (50g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been collected. The yield of (S)-1-(2-benzothiazolyl)-2-hydroxymethylpyrrolidine is 8.8g.

Example 3- To (R)-2-pyrrolidinemethanol (10.1g) in THF (50ml) is added 4,5-dimethylthiazole (14.8g) also in THF (100ml) and then, dropwise, triethylamine (10.1g). Stir at 50°C for 4 hours. Cool to room temperature and filter out the solid. Evaporate the solvent and dissolve the crude product in 10ml of methylene chloride. Pass through a silica plug (100g) in a fritted filter funnel, and elute with methanol/methylene chloride (10:90), applying suction until the product has been 25 collected. The yield of (R)-1-(4,5-dimethyl-2-thiazolyl)-2-hydroxymethylpyrrolidine is 19.5g.

Example 4- 2-chloropyridine (12g) and 2-(methylamino)ethanol (100ml) are stirred under nitrogen at 120°C for 18 hours. Cool to room temperature and then pour into 30 iced water (250ml). Extract with ethyl acetate (2x200ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The crude product is distilled in vacuo to give 10.3g of N-methyl-N-(2-pyridinyl)-2-aminoethanol, boiling at 110°C/1.0mmHg.

Example 5- A solution of 2-chlorobenzoxazole (15.3g) in THF (100ml) is added dropwise to an ice-cold solution of 2-(methylamino)ethanol (8.0g) and triethylamine (10.1g) also in THF (100ml). The mixture is stirred at room temperature for 4 hours and the solid is filtered off. The solvent is evaporated and the residue is dissolved in 5 methylene chloride and passed through a silica plug (100g), eluting with methanol/methylene chloride (10:90) until the product has been collected. The yield of N-methyl-N-(2-benzoxazolyl)-2-aminoethanol is 15.7g.

Example 6- Thionyl chloride (2.5ml) was added dropwise to an ice-cold solution of 10 (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylcarbinol (5.1g) in anhydrous methylene chloride (50ml). The solution was stirred at 0°C for 1 hour and then at room temperature for another period of 2 hours. Wash with saturated sodium bicarbonate solution (2x25ml), then with brine (25ml), and then with water (25ml). Dry over sodium sulfate, filter, and evaporate to dryness. The crude product, (R)-6- 15 hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (5.2g) is used as is in the next step.

Example 7- Thionyl chloride (2.5ml) was added dropwise to an ice-cold solution of 20 (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylcarbinol (5.1g) in anhydrous methylene chloride (50ml). The solution was stirred at 0°C for 1 hour and then at room temperature for another period of 2 hours. Wash with saturated sodium bicarbonate solution (2x25ml), then with brine (25ml), and then with water (25ml). Dry over sodium sulfate, filter, and evaporate to dryness. The crude product, (S)-6- 25 hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (5.0g) is used as is in the next step.

Example 8- A mixture of (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (8.43g), triethylamine (2.6g), and 2-(methylamino)ethanol (40ml) is stirred at 30 120°C under nitrogen for 16 hours. Cool to room temperature and pour into iced water (100ml). Extract with ethyl acetate (3x100ml) and wash the combined organic extracts with brine (100ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The product, (R)-2-[N-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N- methylamino]ethanol weighs 9.0g.

Example 9- A mixture of (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl chloride (8.43g), triethylamine (2.6g), and 2-(methylamino)ethanol (40ml) is stirred at 120°C under nitrogen for 16 hours. Cool to room temperature and pour into iced water (100ml). Extract with ethyl acetate (3x100ml) and wash the combined organic extracts with brine (100ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The product, (S)-2-[N-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethyl)-N-methylamino]ethanol weighs 8.9g.

Example 10- A mixture of 2-chlorobenzoxazole (3.7g), (L)-proline methyl ester, hydrochloride salt (4.0g), and triethylamine (4.9g) in anhydrous THF (50ml) is stirred at room temperature for 18 hours. The solid is filtered off and washed with THF (10ml). The solution is evaporated to dryness and the crude product is dissolved in methylene chloride (5ml) and passed through a plug of silica (50g), eluting with ethyl acetate/methylene chloride (10:90). The product, (L)-N-(2-benzoxazolyl)-proline methyl ester (5.0g) is a crystalline solid.

Example 11- A mixture of 2-chlorobenzoxazole (3.7g), (D)-proline methyl ester, hydrochloride salt (4.0g), and triethylamine (4.9g) in anhydrous THF (50ml) is stirred at room temperature for 18 hours. The solid is filtered off and washed with THF (10ml). The solution is evaporated to dryness and the crude product is dissolved in methylene chloride (5ml) and passed through a plug of silica (50g), eluting with ethyl acetate/methylene chloride (10:90). The product, (D)-N-(2-benzoxazolyl)-proline methyl ester (5.5g) is a crystalline solid.

Example 12- (L)-N-(2-benzoxazolyl)-proline methyl ester (5.0g) is suspended in a mixture consisting of methanol (50ml), water (5ml), and lithium hydroxide (0.5g). Stir for 18 hours at room temperature. Acidify to pH 4.5 with citric acid. Extract with ethyl acetate (4x50ml). Dry over sodium sulfate, filter, and evaporate to dryness. The product, (L)-N-(2-benzoxazolyl)-proline (4.3g) is an off-white solid.

Example 13- A mixture of (L)-proline (4.6g), 2-chlorobenzoxazole (6.6g), and triethylamine (4.45g) in anhydrous THF (100ml) is stirred at reflux temperature for 18 hours. Cool down to room temperature, filter off the solid and wash it with a THF (10ml). Evaporate the solvent. Add ethyl acetate (50ml) and then 1N sodium

hydroxide (50ml). Stir for 5 minutes. Keep the aqueous phase. Wash again with ethyl acetate (50ml). Acidify with citric acid to pH 4.5. Isolate the precipitate by filtration. The aqueous filtrate is extracted with ethyl acetate (4x30ml). Dry over sodium sulfate. Filter. Evaporate to dryness. The solids are dried in vacuo at 35°C
5 for 18 hours. The first crop of product weighs 4.77g. The second crop weighs 3.26g. The total amount of product, (L)-N-(2-benzoxazolyl)-proline, is 8.03g.

Example 14- A mixture of (D)-proline (4.6g), 2-chlorobenzoxazole (6.6g), and triethylamine (4.45g) in anhydrous THF (100ml) is stirred at reflux temperature for 18
10 hours. Cool down to room temperature, filter off the solid and wash it with a THF (10ml). Evaporate the solvent. Add ethyl acetate (50ml) and then 1N sodium hydroxide (50ml). Stir for 5 minutes. Keep the aqueous phase. Wash again with ethyl acetate (50ml). Acidify with citric acid to pH 4.5. Isolate the precipitate by filtration. The aqueous filtrate is extracted with ethyl acetate (4x30ml). Dry over
15 sodium sulfate. Filter. Evaporate to dryness. The solids are dried in vacuo at 35°C for 18 hours. The first crop of product weighs 4.93g. The second crop weighs 2.90g. The total amount of product, (L)-N-(2-benzoxazolyl)-proline, is 7.83g.

Example 15- A mixture of 4-hydroxybenzaldehyde (122.12g), 2,4-thiazolidinedione
20 (117.13g), piperidine (5.11g), and benzoic acid (6.11g) in toluene (1,000ml), is stirred at 80°C for 16 hours. Cool to room temperature and filter off the yellow solid. Wash the solid with methylene chloride (3x100ml) and then with methanol/methylene chloride (30:70) (2x100ml). Dry in vacuo at 35°C until constant weight. The yield of product, 5-(4-hydroxybenzylidene)-2,4-thiazolidinedione, is 217.8g.
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Example 16- To p-anisidine (25g) in acetone (400ml) at between 0 and 5°C, add dropwise a solution of sodium nitrite (15.41g) in water (50ml) and 12N hydrochloric acid (50ml) from 2 different funnels over a 15-minute period. Stir for another 5 minutes at 0°C. Add methyl acrylate (104.9g) and then warm up the solution to 35°C.
30 Transfer into a 2-L Erlenmeyer flask and stir vigorously. While stirring, add copper(I) oxide (0.7g) in several portions. Keep stirring for as long as nitrogen gas evolves from the solution, then stir for another 4 hours. Evaporate the organic solvent and dilute the aqueous residue with water (200ml). Extract with methylene chloride

(200ml). Dry over sodium sulfate, filter, and evaporate to dryness. The product, methyl 2-chloro-3-(4-methoxyphenyl)propanoate, is a dark oil weighing 42.96g.

Example 17- Methyl 2-chloro-3-(4-methoxyphenyl)propanoate (31.44g), thiourea 5 (16.89g), and anhydrous sodium acetate (11.24g) in 2-methoxyethanol (100ml) is stirred at 100°C for 4 hours. Cool to room temperature and place the flask at 4°C for 16 hours. The pale yellow solid is filtered off and is washed with hexanes (50ml). Stir for 30 minutes in ethyl acetate/water (100ml:10ml). Filter. Crystallize from hot ethanol (600ml). After leaving at 4°C for 16 hours, the crystals are filtered off and 10 stirred at reflux for 8 hours in a mixture of 2-methoxyethanol (100ml) and 2N hydrochloric acid (20ml). Evaporate the solvent. Add ethyl acetate (200ml) and water (200ml). Keep the organic phase and wash again with water (200ml). Dry over sodium sulfate, filter, evaporate to dryness. The product, 5-(4-methoxybenzyl)thiazolidine-2,4-dione (16.7g) is an oil that solidifies upon standing.

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Example 18- To a solution of 5-(4-methoxybenzyl)thiazolidine-2,4-dione (14.3g) in anhydrous methylene chloride (100ml) cooled to -40°C, add a 1.0M solution of boron tribromide in methylene chloride (63ml). The solution is left to warm up to 23°C and is then stirred for another 16 hours. Pour into iced water (700ml) and stir for 15 20 minutes. Isolate the precipitate by filtration. Wash the product with water (50ml) and then with methylene chloride (50ml). The yield of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione is 12.8g.

Example 19- A mixture of methyl 4-formylbenzoate (164.16g), 2,4-thiazolidinedione 25 (117.13g), piperidine (5.11g), and benzoic acid (6.11g) in toluene (1,000ml), is stirred at 80°C for 16 hours. Cool to room temperature and filter off the yellow solid. Wash the solid with methylene chloride (3x100ml) and then with methanol/methylene chloride (30:70) (2x100ml). Dry in vacuo at 35°C until constant weight. The yield of product, 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione, is 258.0g.

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Example 20- A suspension of 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione (26.3g) and magnesium turnings (24g) in anhydrous methanol (300ml) is stirred at 45°C for 8 hours. Acidify to pH 5.0 with 6N HCl and then extract with methylene chloride (2x250ml). Dry over sodium sulfate, filter, and evaporate to dryness. The

crude product is chromatographed on silica gel (1,300g), eluting with methanol/methylene chloride (02:98). The yield of 5-(4-carbomethoxybenzyl)-2,4-thiazolidinedione is 15.2g.

- 5 Example 21- A suspension of 5-(4-carbomethoxybenzylidene)-2,4-thiazolidinedione (50g) in 6N HCl (200ml) is stirred at reflux for 4 hours. The mixture is cooled to 4°C and the product is filtered off. The product is then washed with water (2x100ml) and is dried in vacuo at 40°C. The yield of 5-(4-carboxybenzylidene)-2,4-thiazolidinedione is 45g.

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- Example 22- A suspension of 5-(4-carbomethoxybenzyl)-2,4-thiazolidinedione (50g) in 6N HCl (200ml) is stirred at reflux for 4 hours. The mixture is cooled to 4°C and the product is filtered off. The product is then washed with water (2x100ml) and is dried in vacuo at 40°C. The yield of 5-(4-carboxybenzyl)-2,4-thiazolidinedione is
15 44g.

- Example 23- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (9.2g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (8.3g) are dissolved in methylene chloride (100ml) and THF (50ml). To this add dicyclohexylcarbodiimide (7.6g) and DMAP
20 (0.5g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (20ml). The solvent is removed and the solid residue is stirred with methylene chloride (100ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzyl}thiazolidine-2,4-dione is 12.4g.
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- Example 24- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (9.2g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (8.3g) are dissolved in methylene chloride (100ml) and THF (50ml). To this add dicyclohexylcarbodiimide (7.6g) and DMAP
30 (0.5g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (20ml). The solvent is removed and the solid residue is stirred with methylene chloride (100ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of

5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzyl}thiazolidine-2,4-dione is 13.3g.

Example 25- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (1.9g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (1.8g) are dissolved in methylene chloride (20ml) and THF (10ml). To this add dicyclohexylcarbodiimide (1.6g) and DMAP (0.1g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (5ml). The solvent is removed and the solid residue is stirred with methylene chloride (20ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyl}thiazolidine-2,4-dione is 2.54g.

Example 26- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (1.9g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (1.8g) are dissolved in methylene chloride (20ml) and THF (10ml). To this add dicyclohexylcarbodiimide (1.6g) and DMAP (0.1g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (5ml). The solvent is removed and the solid residue is stirred with methylene chloride (20ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzyl}thiazolidine-2,4-dione is 2.17g.

Example 27- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (4.6g) and 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (4.2g) are dissolved in methylene chloride (50ml) and THF (25ml). To this add dicyclohexylcarbodiimide (3.8g) and DMAP (0.25g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (50ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzylidene}thiazolidine-2,4-dione is 5.9g.

Example 28- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (4.6g) and 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (4.2g) are dissolved in methylene chloride (50ml) and THF (25ml). To this add dicyclohexylcarbodiimide (3.8g) and DMAP (0.25g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (50ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy]benzylidene}thiazolidine-2,4-dione is 6.2g.

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Example 29- (R)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (3.8g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.6g) are dissolved in methylene chloride (40ml) and THF (20ml). To this add dicyclohexylcarbodiimide (3.2g) and DMAP (0.2g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (40ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene}thiazolidine-2,4-dione is 5.4g.

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Example 30- (S)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carbinol (3.8g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.6g) are dissolved in methylene chloride (40ml) and THF (20ml). To this add dicyclohexylcarbodiimide (3.2g) and DMAP (0.2g), and then stir for 4 hours at room temperature. The solid is removed by filtration and is washed with a small amount of THF (10ml). The solvent is removed and the solid residue is stirred with methylene chloride (40ml) and left at 4°C for 16 hours. The product is isolated by filtration and dried in vacuo at 23°C. The yield of 5-{4-[(S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-methoxy]benzylidene}thiazolidine-2,4-dione is 5.2g.

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Example 31- (L)-N-(2-benzoxazolyl)-proline (3.26g) and 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (3.11g) are suspended in methylene chloride (100ml). Add DCC (2.89g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 114g of silica, eluting with methanol/methylene chloride

(02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidine-2-carboxy]benzyl}thiazolidine-2,4-dione is 4.55g.

Example 32- (L)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (3.25g) are suspended in methylene chloride (100ml). Add DCC (2.88g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 132g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzyl}-thiazolidine-2,4-dione is 4.68g.

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Example 33- (D)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzylidene)thiazolidine-2,4-dione (3.35g) are suspended in methylene chloride (100ml). Add DCC (2.91g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 108g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(R)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzylidene}-thiazolidine-2,4-dione is 4.32g.

20

Example 34- (D)-1-(2-benzoxazolyl)pyrrolidine-2-carbinol (3.26g) and 5-(4-carboxybenzyl)thiazolidine-2,4-dione (3.25g) are suspended in methylene chloride (100ml). Add DCC (2.93g) and DMAP (0.12g) and stir at room temperature for 4 hours. Filter and purify on 162g of silica, eluting with methanol/methylene chloride (02:98). The yield of 5-{4-[(S)-1-(2-benzoxazolyl)pyrrolidinyl-2-methoxycarbonyl]benzyl}-thiazolidine-2,4-dione is 4.77g.

25

Example 35- Triethylamine (8.3ml) is added dropwise to a stirred cold solution of ethyl 2-aminoacetoacetate hydrochloride (5.4g) and 4-methoxybenzoyl chloride (5.2g) in dichloromethane (100ml). After stirring for 3 hours, the solution is washed with water (100ml), dried over sodium sulfate, filtered, and evaporated to dryness. The crude product, ethyl 2-(4-methoxy)phenylaminoacetoacetate weighs 6.7g.

30

Example 36- Ethyl 2-(4-methoxy)phenylaminoacetoacetate (5.9g) and phosphorus oxychloride (50ml) are stirred at 100C for 30 minutes. The phosphorus oxychloride is removed by evaporation, and the residue is diluted with aqueous sodium bicarbonate and extracted with methylene chloride. After drying over sodium sulfate, the solution

is evaporated and the product is crystallized from hexane, giving ethyl 5-methyl-2-(4-methoxy)phenyl-4-oxazolecarboxylate (4.5g).

Example 37- A solution of benzoyl chloride (17g) in ethyl acetate (40ml) is added dropwise, with stirring, in an ice-cold mixture of L-serine methyl ester, hydrochloride (15.5g), water (100ml), sodium bicarbonate (21.8g), and ethyl acetate (100ml). After stirring for 2 hours, the organic phase is separated, dried over sodium sulfate, and evaporated to give crystalline N-benzoyl-L-serine methyl ester (22.0g).

- 10 Example 38- A stirred mixture of N-benzoyl-L-serine methyl ester (21.0g), thionyl chloride (21.0g), and methylene chloride (150ml) is stirred at reflux for 1 hour. The solvent is evaporated and the residue is diluted with cold water. Neutralize with sodium bicarbonate, and extract with ethyl acetate. Purification on silica gel (250g), eluting with methanol:methylene chloride (01:99), yields methyl (S)-2-phenyl-2-oxazoline-4-carboxylate (15.2g).
- 15

Example 39- A solution of benzoyl chloride (17g) in ethyl acetate (40ml) is added dropwise, with stirring, in an ice-cold mixture of L-threonine methyl ester, hydrochloride (16.5g), water (100ml), sodium bicarbonate (21.8g), and ethyl acetate (100ml). After stirring for 2 hours, the organic phase is separated, dried over sodium sulfate, and evaporated to give crystalline N-benzoyl-L-threonine methyl ester (21.5g).

Example 40- A stirred mixture of N-benzoyl-L-threonine methyl ester (21.0g), thionyl chloride (21.0g), and methylene chloride (150ml) is stirred at reflux for 1 hour. The solvent is evaporated and the residue is diluted with cold water. Neutralize with sodium bicarbonate, and extract with ethyl acetate. Purification on silica gel (250g), eluting with methanol:methylene chloride (01:99), yields methyl (R,S)-2-phenyl-2-oxazoline-5-methyl-4-carboxylate (14.8g).

- 30 Example 41- Activity in NIDDM KK-A^y male mice. Non-insulin dependent diabetic mellitus male mice, weighing 50 +/- 5g (9-10 weeks of age) were used. These animals exhibited hyperinsulinemia, hyperglycemia, and islet atrophy. The test compounds 105, 115, and 155, and the positive control compound troglitazone were

suspended in a 1% carboxymethylcellulose preparation and were given orally at a dose of 10mg/kg, twice a day, for 5 consecutive days. Blood sampling was performed before the first dose and then 90 minutes after the last dose. Serum glucose and insulin levels were measured. Percent reduction of serum glucose and insulin levels relative to the pre-treatment values are shown in Table XX and figures 20 and 21.

It should be understood that the reaction schemes and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Formula I

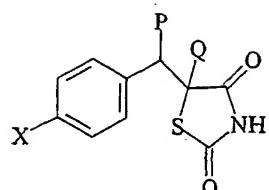


Table I.

Compound number	X	P and Q*
1	HO	H
2		db
3	O	H
4	HO	db
5		H
6		db
7		H
8		db

Table I (continued).

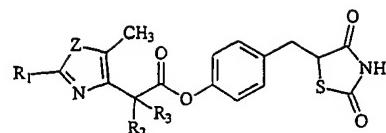
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9		H
10		db
11		H
12		db
13		H
14		db
15		H
16		db

Compound number	X	P and Q*
17		H
18		db
19		H
20		db
21		H
22		db
23		H
24		db

Compound number	X	P and Q*
25		H
26		db
27		H
28		db
29		H
30		db
31		H
32		db

Table II.

Formula II



Compound number	Z	R1	R2	R3
33	O		H	H
34	O		CH3	H
35	O		CH3	CH3
36	S		CH3	H
37	O		CH3	H
38	S		CH3	H
39	O		CH3	H
40	S		CH3	H
41	O		CH3	H

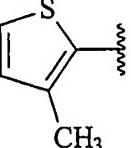
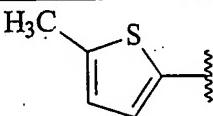
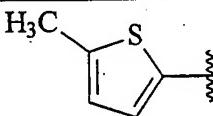
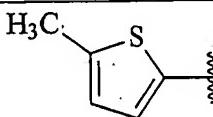
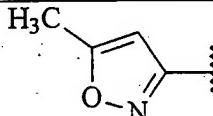
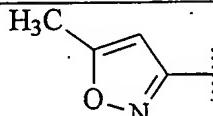
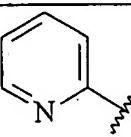
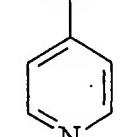
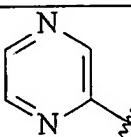
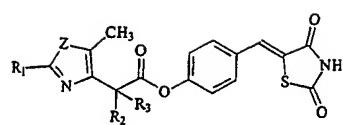
Compound number	Z	R1	R2	R3
42	S		CH3	H
43	O		H	H
44	O		CH3	H
45	S		H	H
46	O		CH3	H
47	S		H	H
48	O		CH3	H
49	O		CH3	H
50	O		CH3	H

Table III.

Compound number	Z	R1	R2	R3
51	O		H	H
52	O		CH3	H
53	O		CH3	CH3
54	S		CH3	H
55	O		CH3	H
56	S		CH3	H
57	O		CH3	H
58	S		CH3	H
59	O		CH3	H

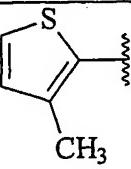
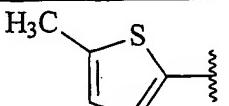
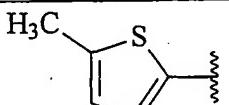
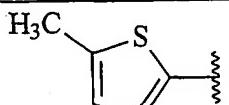
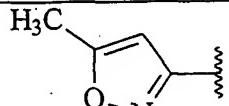
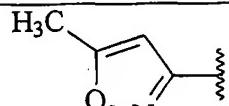
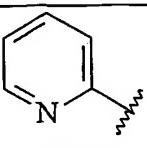
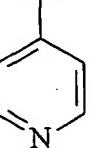
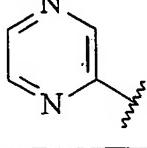
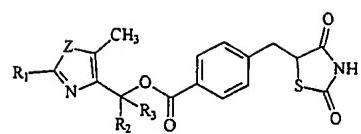
Compound number	Z	R1	R2	R3
60	S		CH3	H
61	O		H	H
62	O		CH3	H
63	S		H	H
64	O		CH3	H
65	S		H	H
66	O		CH3	H
67	O		CH3	H
68	O		CH3	H

Table IV.



Compound number	Z	R1	R2	R3
69	O		H	H
70	O		CH3	H
71	O		CH3	CH3
72	S		CH3	H
73	O		CH3	H
74	S		CH3	H
75	O		CH3	H
76	S		CH3	H
77	O		CH3	H

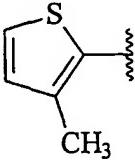
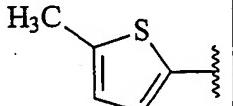
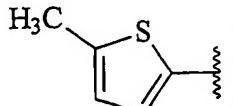
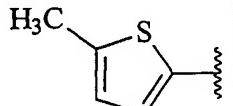
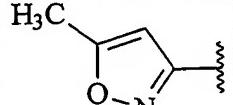
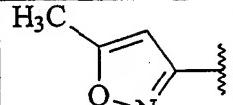
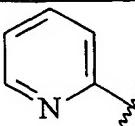
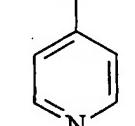
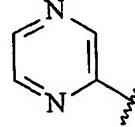
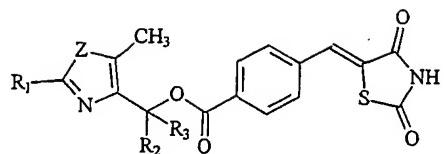
Compound number	Z	R1	R2	R3
78	S		CH3	H
79	O		H	H
80	O		CH3	H
81	S		H	H
82	O		CH3	H
83	S		H	H
84	O		CH3	H
85	O		CH3	H
86	O		CH3	H

Table V



Compound number	Z	R1	R2	R3
87	O		H	H
88	O		CH3	H
89	O		CH3	CH3
90	S		CH3	H
91	O		CH3	H
92	S		CH3	H
93	O		CH3	H
94	S		CH3	H
95	O		CH3	H

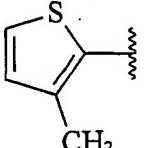
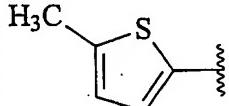
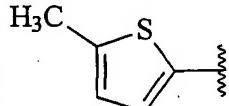
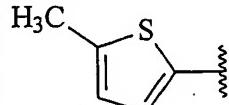
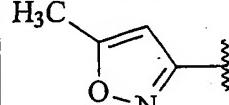
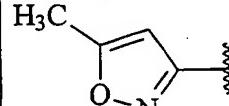
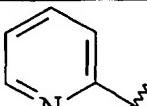
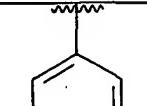
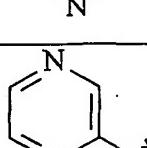
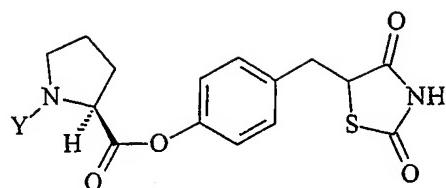
Compound number	Z	R1	R2	R3
96	S		CH3	H
97	O		H	H
98	O		CH3	H
99	S		H	H
100	O		CH3	H
101	S		H	H
102	O		CH3	H
103	O		CH3	H
104	O		CH3	H

Table VI.



Compound number	Y
105	
106	
107	
108	
109	

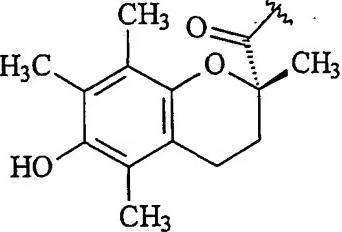
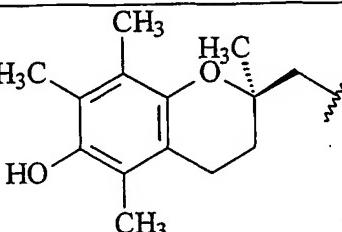
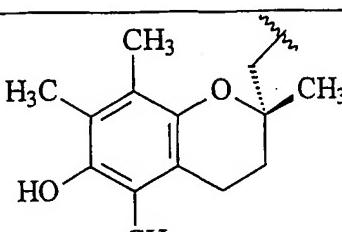
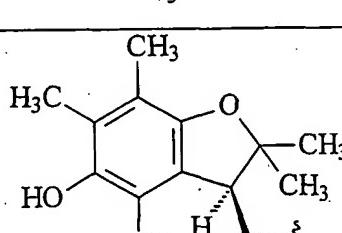
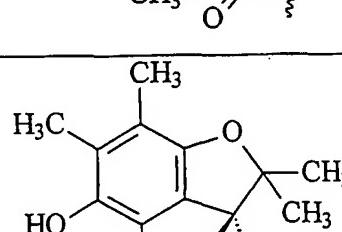
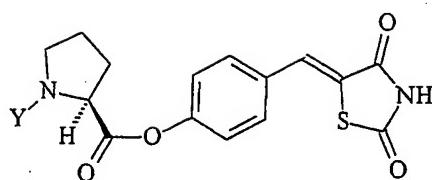
Compound number	Y
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111	
112	
113	
114	

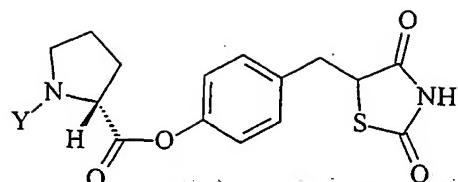
Table VII.



Compound number	Y
115	
116	
117	
118	
119	

Compound number	Y
120	
121	
122	
123	
124	

Table VIII.



Compound number	Y
125	
126	
127	
128	
129	

Compound number	Y
130	
131	
132	
133	
134	

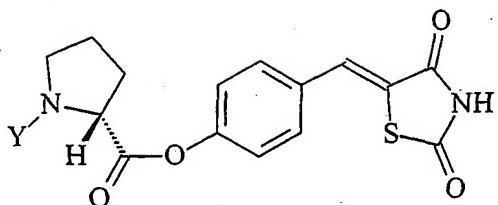


Table IX.

Compound number	Y
135	
136	
137	
138	
139	

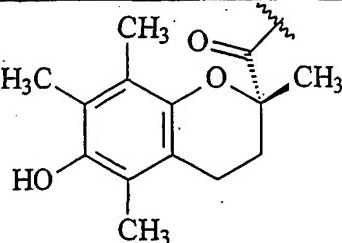
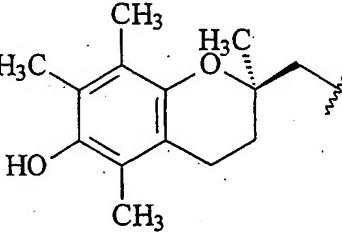
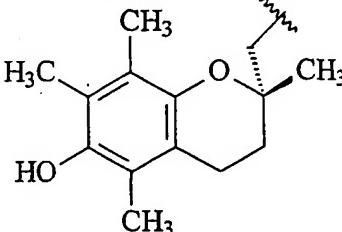
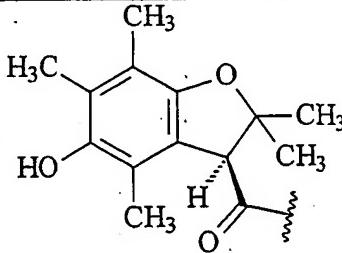
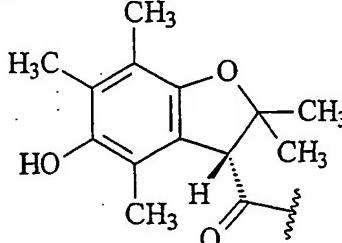
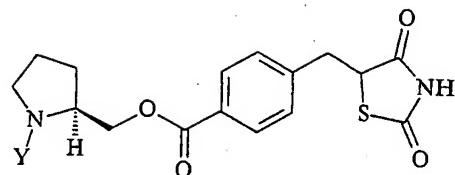
Compound number	Y
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141	
142	
143	
144	

Table X.



Compound number	Y
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146	
147	
148	
149	

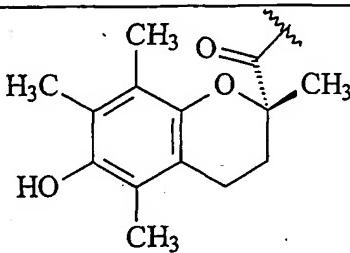
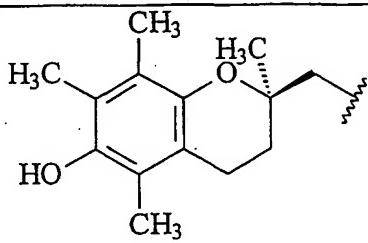
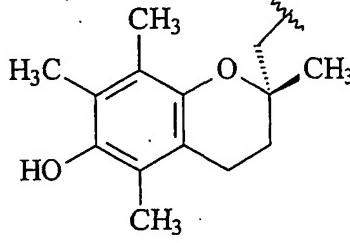
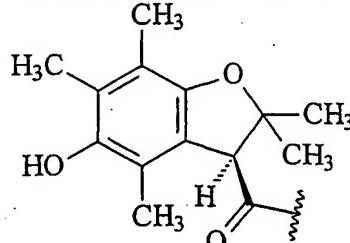
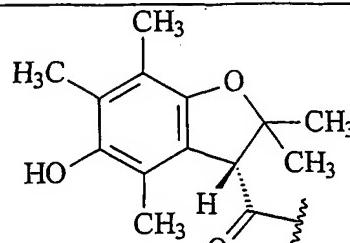
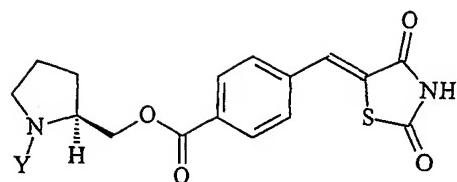
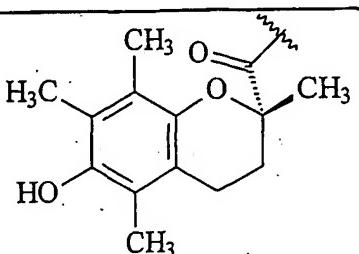
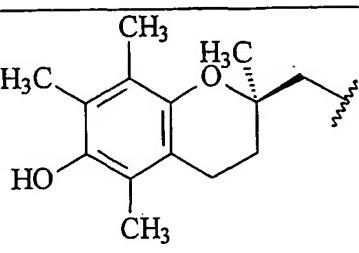
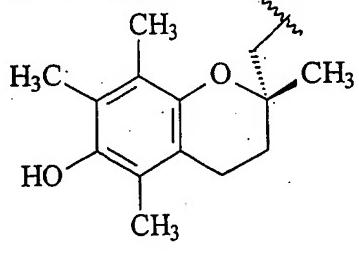
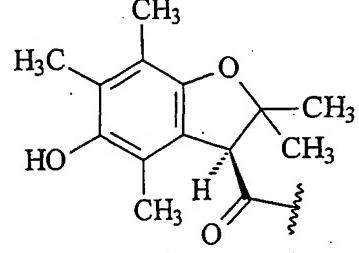
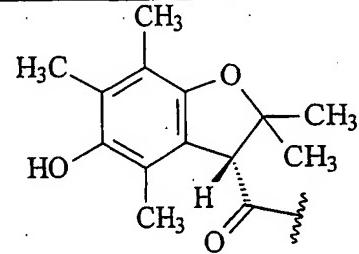
Compound number	Y
150	
151	
152	
153	
154	

Table XI.



Compound number	Y
155	
156	
157	
158	
159	

Compound number	Y
160	
161	
162	
163	
164	

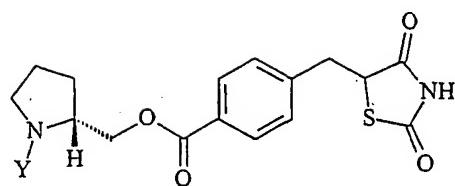
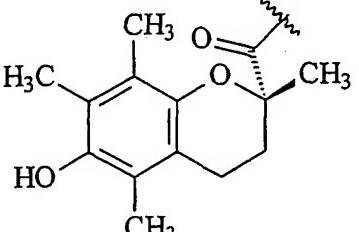
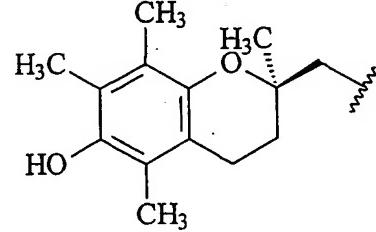
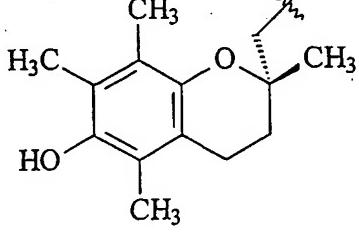
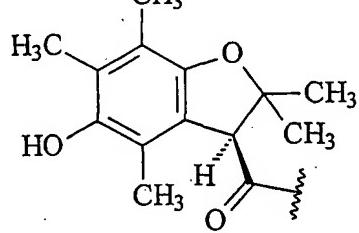
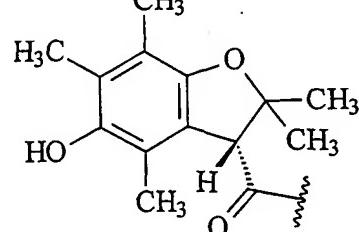


Table XII.

Compound number	Y
165	
166	
167	
168	
169	

Compound number	Y
170	
171	
172	
173	
174	

65

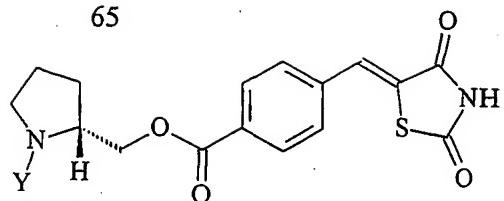
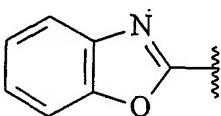
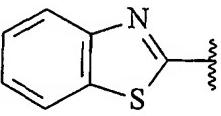
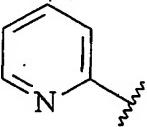
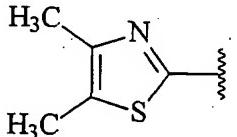
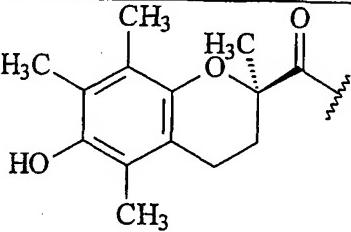


Table XIII.

Compound number	Y
175	
176	
177	
178	
179	

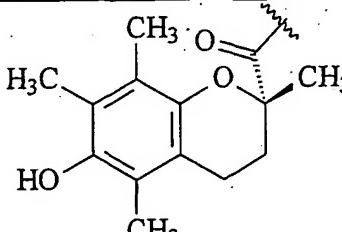
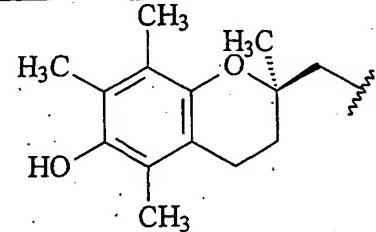
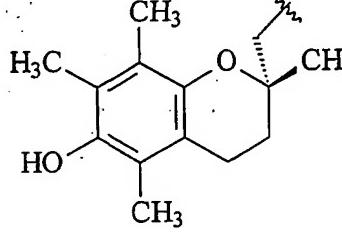
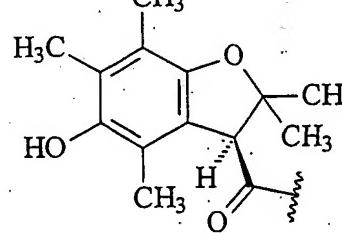
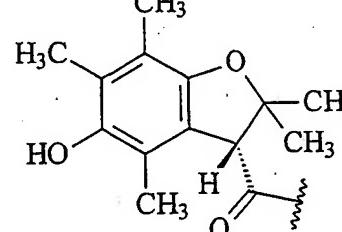
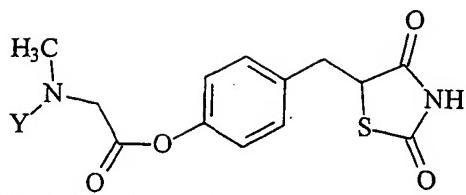
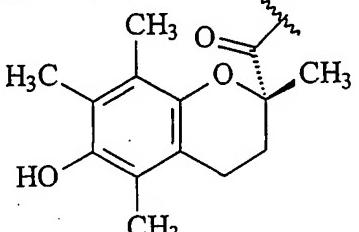
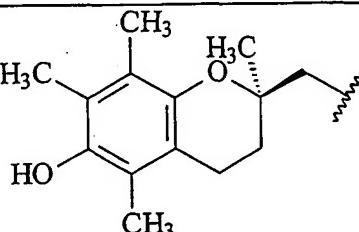
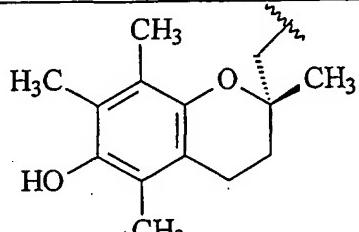
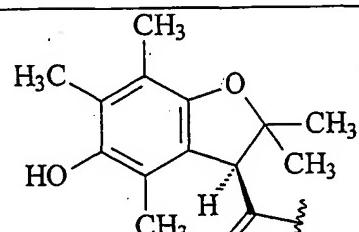
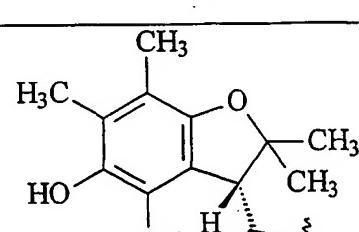
Compound number	Y
180	
181	
182	
183	
184	

Table XIV.



Compound number	Y
185	
186	
187	
188	
189	

Compound number	Y
190	
191	
192	
193	
194	

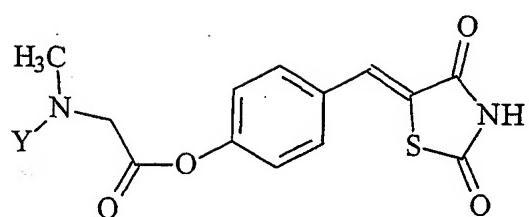


Table XV.

Compound number	Y
195	
196	
197	
198	
199	

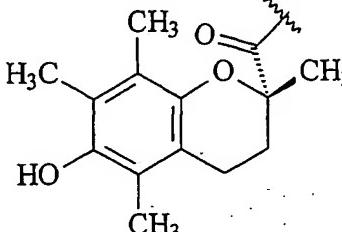
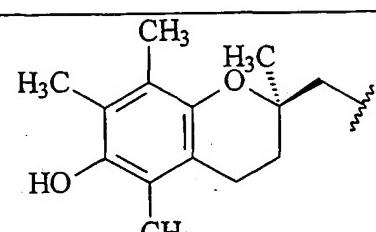
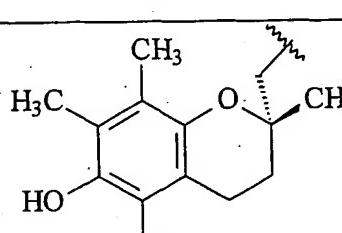
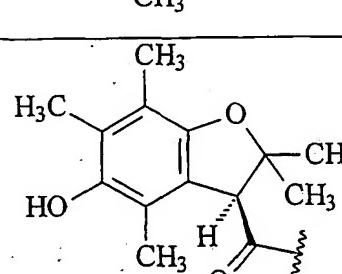
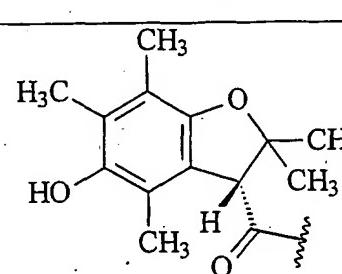
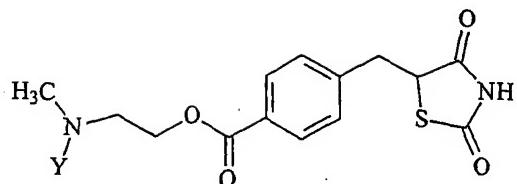
Compound number	Y
200	
201	
202	
203	
204	

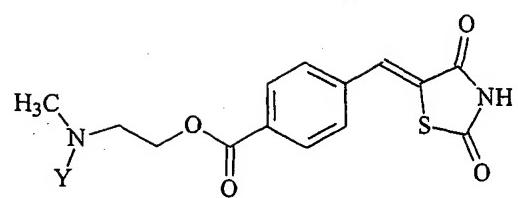
Table XVI.



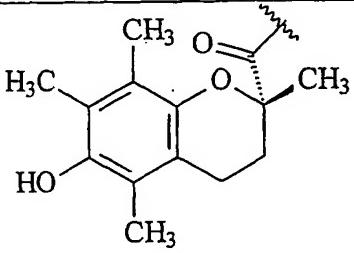
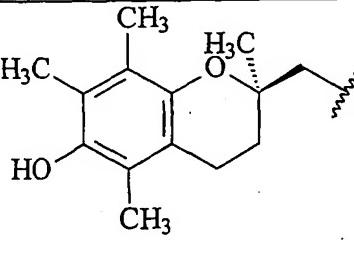
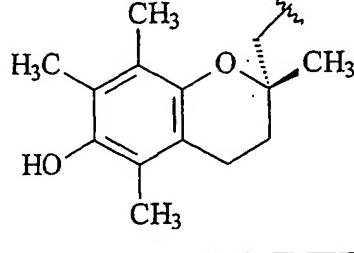
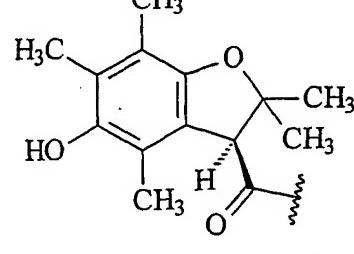
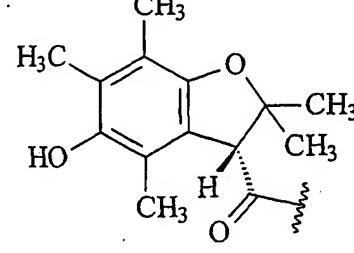
Compound number	Y
205	
206	
207	
208	
209	

Compound number	Y
210	
211	
212	
213	
214	

Table XVII.



Compound number	Y
215	
216	
217	
218	
219	

Compound number	Y
220	
221	
222	
223	
224	

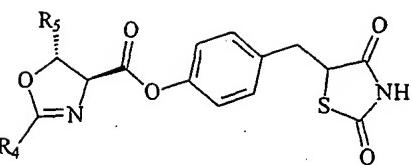
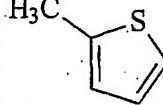
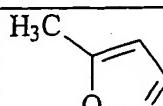
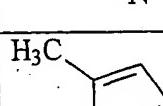
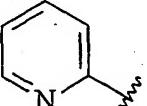
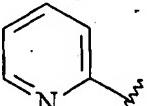
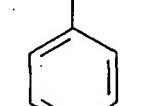
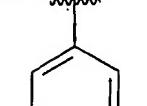
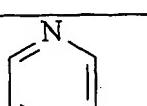
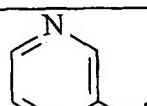


Table XVIII.

Compound number	R4	R5
225		H
226		CH3
227		H
228		CH3
229		H
230		CH3
231		H
232		CH3
233		H

Compound number	R4	R5
234		CH3
235		H
236		CH3
237		H
238		CH3
239		H
240		CH3
241		H
242		CH3

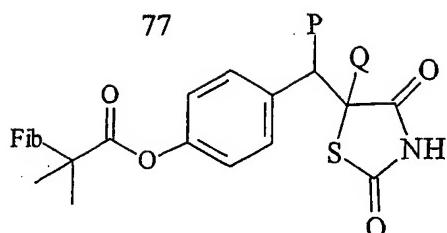


Table XIX.

Compound number	Fib	P and Q*
243		H
244		db
245		H
246		db
247		H
248		db

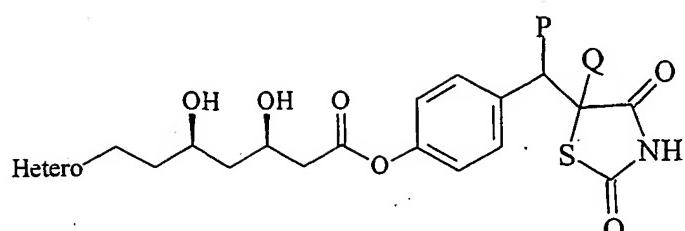


Table XX.

Compound number	Hetero	P and Q*
249		H
250		db
251		H
252		db

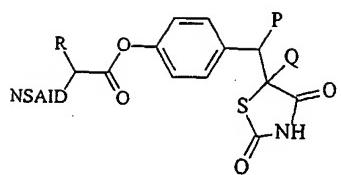
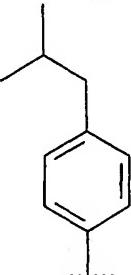
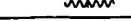
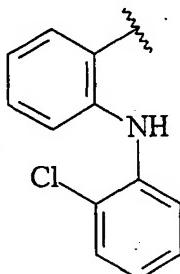
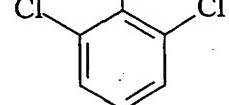


Table XXI

Compound number	NSAID	P and Q*
253		H
254		db
255		H
256		db

Table XXI (continued)

Compound number	NSAID	P and Q*
257		H
258		db
259		H
260		db

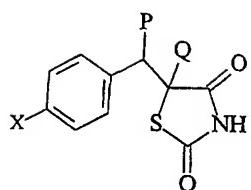


Table XXII

Compound number	X	P and Q*
261		H
262		db
263		H
264		db

Table XXII (continued)

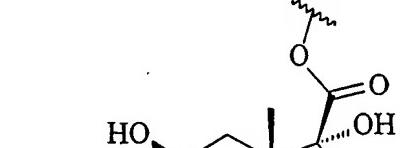
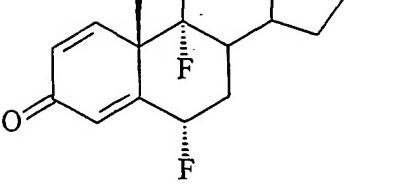
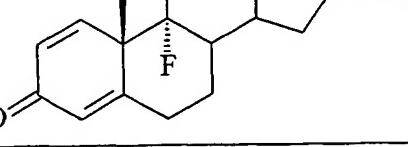
Compound number	X	P and Q*
265		H
266		db
267		H
268		db

Table XXIII: Activity in NIDDM Mice.

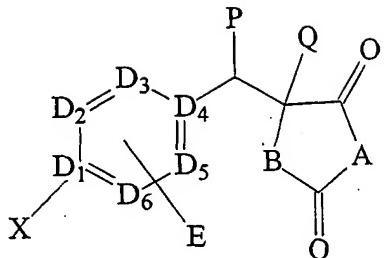
Compound	Serum Glucose (%)	Serum Insulin (%)
Vehicle	0	1
105	40	10
115	36	13
155	37	9
Troglitazone	35	15

Claims

We claim:

1. A compound comprising

Formula I



wherein:

A and B may be the same or different and are C, N, NO, NH, SO₀₋₂, or O;

D₁-D₆ can be the same or different and are C, N, S, or O;

E can be attached to one or more of the atoms located at D₁-D₆;

P and Q can be a double bond; or

P, Q, and E can be the same or different and are a moiety selected from the group consisting of H, C₁₋₁₀ alkyl, substituted alkyl groups, substituted or unsubstituted carboxylic acids, substituted or unsubstituted carboxylic esters, halogen, carboxyl, hydroxyl, phosphate, phosphonate, aryl, CN, OH, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄;

X is -OH, -COOH, or a substituted carboxylic group comprising OOC- or COO- and said substituted carboxylic group is attached to D₁;

and analogs, derivatives, or salts of the compound according to Formula I.

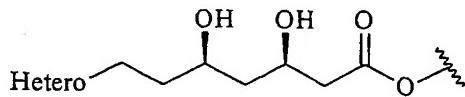
2. The compound according to claim 1, wherein said substituted carboxylic acid group is substituted with a moiety selected from the group consisting of alkyloxycarbonyl, alkylcarbonyloxy, aryloxycarbonyl, arylcarbonyloxy, heteroalkyloxycarbonyl, heteroalkylcarbonyloxy, heteroaryl-oxycarbonyl,

heteroarylcarbonyloxy, each of which is, optionally, substituted with C₁₋₁₀ alkyl, CN, COOH, NO₂, NH₂, SO₂₋₄, C₁₋₂₀ heteroalkyl, C₂₋₂₀ alkenyl, alkynyl, alkynyl-aryl, alkynyl-heteroaryl, aryl, C₁₋₂₀ alkyl-aryl, C₂₋₂₀ alkenyl-aryl, heteroaryl, C₁₋₂₀ alkyl-heteroaryl, C₂₋₂₀ alkenyl-heteroaryl, cycloalkyl, heterocycloalkyl, C₁₋₂₀ alkyl-heterocycloalkyl, and C₁₋₂₀ alkyl-cycloalkyl, any of which may be, optionally, substituted with a moiety selected from the group consisting of C₁₋₆ alkyl, halogen, OH, NH₂, CN, NO₂, COOH, or SO₂₋₄.

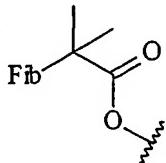
3. The compound according to claim 1, wherein said heterocyclic groups are selected from the group consisting of morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine or thiadiazoline.

4. The compound according to claim 2, wherein said heterocyclic groups are selected from the group consisting of morpholine, triazole, imidazole, pyrrolidine, piperidine, piperazine, pyrrole, dihydropyridine, aziridine, thiazolidine, thiazoline, thiadiazolidine, and thiadiazoline.

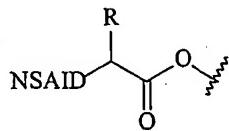
5. The compound according to claim 1, wherein X is hydroxyl; hydroxycarbonyl; 1-methyl-1-cyclohexylcarbonyloxy; 1-methyl-1-cyclohexylmethoxycarbonyl; 5-ethyl-2-pyridylacetoxyl; 5-ethyl-2-pyridylmethoxycarbonyl; (R)-6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxy; (S)-6-hydroxy-2,5,7,8-tetra-methylchroman-2-carboxy; (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl; (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl; (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy; (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy; (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl; (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl; 2-hydroxybenzoyloxy; 2,4-dihydroxybenzoyloxy;



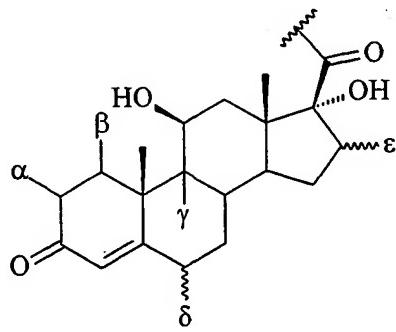
wherein Hetero is an aromatic, cyclic, or alicyclic moiety, or an aromatic, cyclic, or alicyclic moiety that contains heteroatoms that are part of the structure of the statin-family of lipid lowering agents;



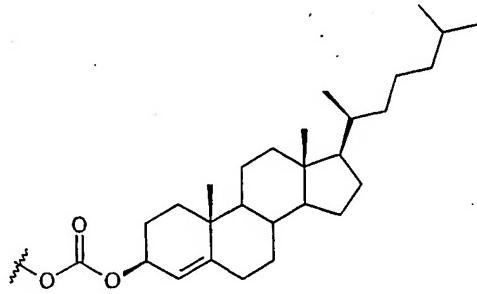
wherein Fib is an aromatic, cyclic, an alicyclic moiety contains heteroatoms or a portion of the fibrate molecule;

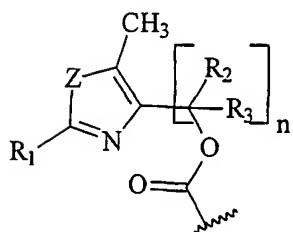
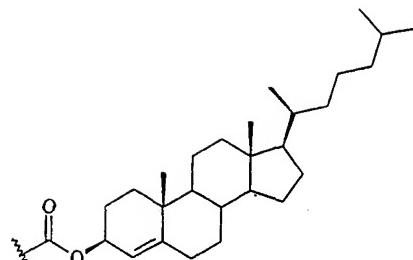


wherein R is hydrogen or methyl, and in which NSAID is an aromatic, alkyl, or cycloalkyl moiety that contains heteroatoms;

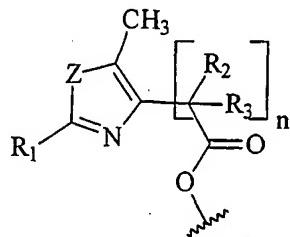


wherein α and β are hydrogen or α and β form a bond, and wherein γ , δ , and ϵ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl;



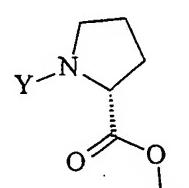
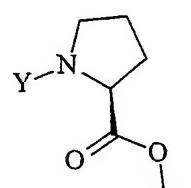
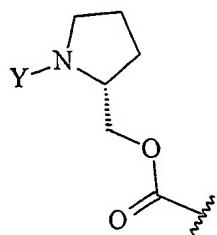
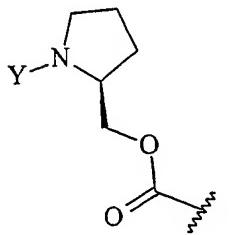


wherein n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl;

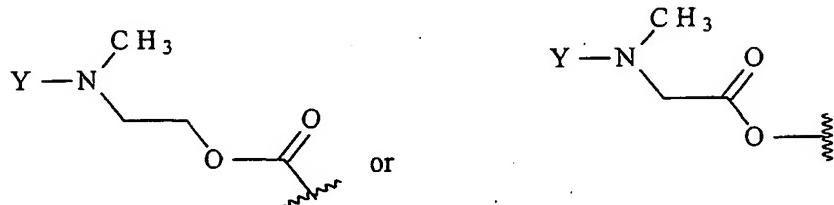


wherein n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl;

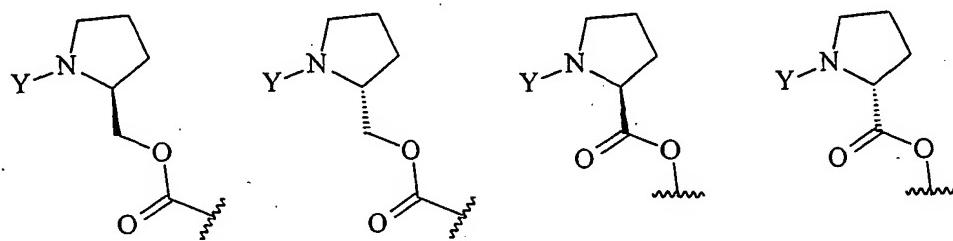
1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas:



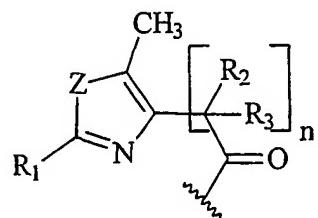
wherein Y is aryl, heteroaryl, alkyl, or heteroalkyl;
 N-substituted 2-methylaminoethoxycarbonyl or a N-substituted 2-methylamino-acetoxy, having the following formulas:



wherein Y is aryl, heteroaryl, alkyl, or heteroalkyl;
 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas:

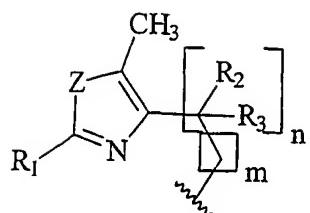


wherein Y is



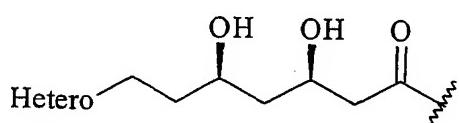
n is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl; or

Y is



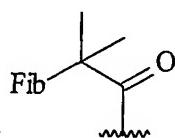
n is 0 or 1; m is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl; or

Y is



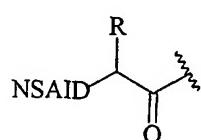
wherein Hetero is an aromatic, cyclic, or alicyclic moiety; or

Y is



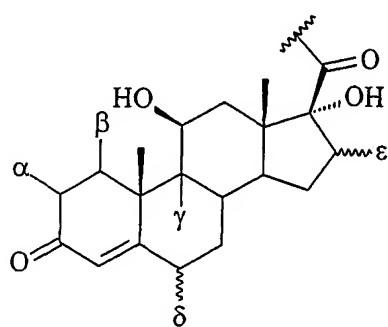
wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms; or

Y is



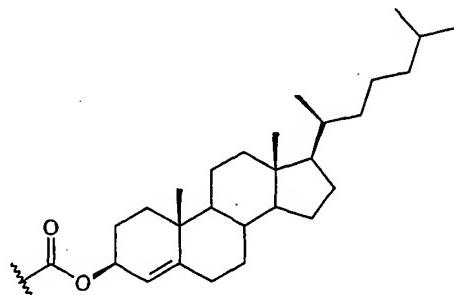
wherein R is hydrogen or methyl and NSAID is an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms; or

Y is

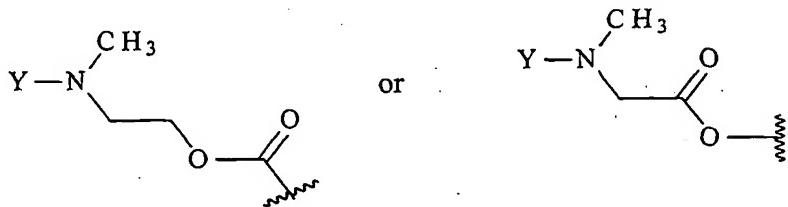


wherein α and β are hydrogen or α and β form a bond, and wherein γ , δ , and ε , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

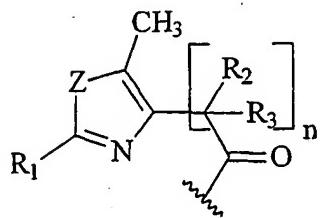
Y is



N-substituted 2-methylaminoethoxycarbonyl or an N-substituted 2-methylaminoacetoxy, having the following formulas:

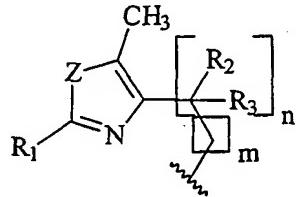


wherein Y is



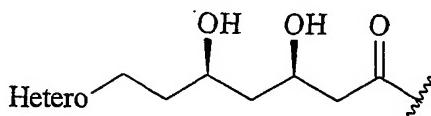
n is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl; or

Y is



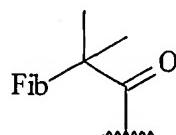
n is 0 or 1; m is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl or heteroaryl, alkyl or heteroalkyl; or

Y is



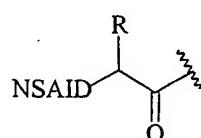
wherein Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms; or

Y is



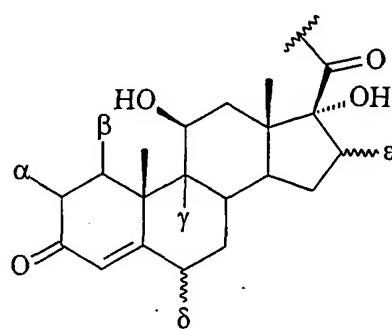
wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms; or

Y is



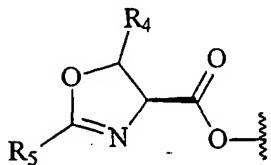
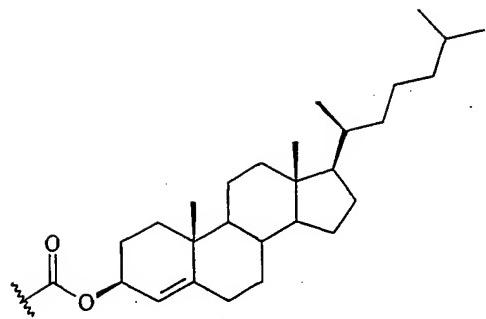
wherein R is hydrogen or methyl, and in which NSAID is an aromatic, alkyl, or cycloalkyl moiety; or

Y is

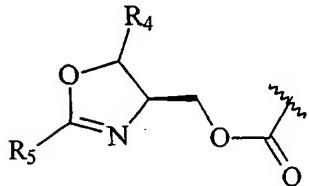


wherein α and β are hydrogen or α and β form a bond, and wherein γ, δ, and ε, are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

Y is



wherein R₄ is hydrogen or methyl, and wherein R₅ is aryl, heteroaryl, alkyl, or heteroalkyl; or



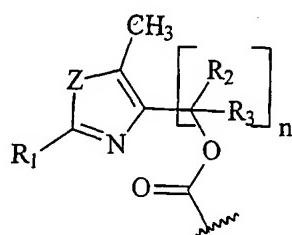
wherein R₄ is hydrogen or methyl, and wherein R₅ is aryl, heteroaryl, alkyl, or heteroalkyl.

6. The compound according to claim 5, wherein said heteroatom containing statin structure is 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl or 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl.

7. The compound according to claim 5, wherein said Fib moieties are 4-(4-chlorobenzoyl)phenoxy, 4-chlorophenoxy, or 3-(2,5-xylyloxy)-1-propyl.

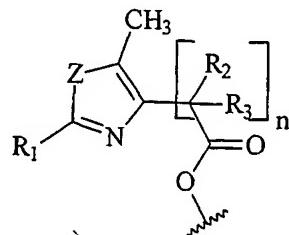
8. The compound according to claim 5, wherein said NSAID moieties are 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, or 6'-methoxy-2'-naphthylmethyl.

9. The compound according to claim 5, wherein X is



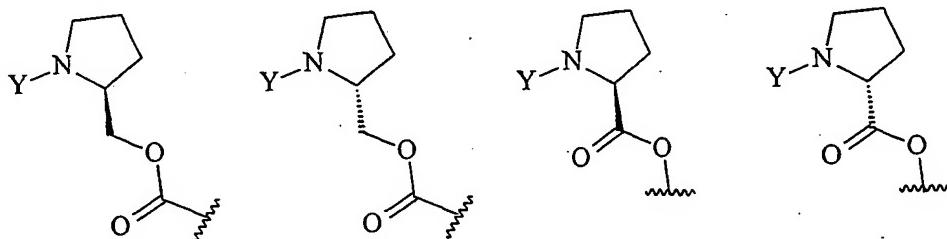
wherein n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

10. The compound according to claim 5, wherein X is



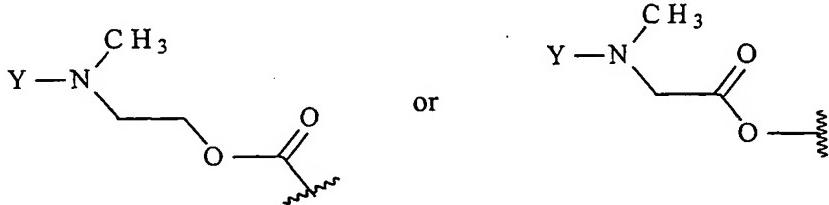
n is 0 or 1, R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

11. The compound according to claim 5, wherein X is a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas



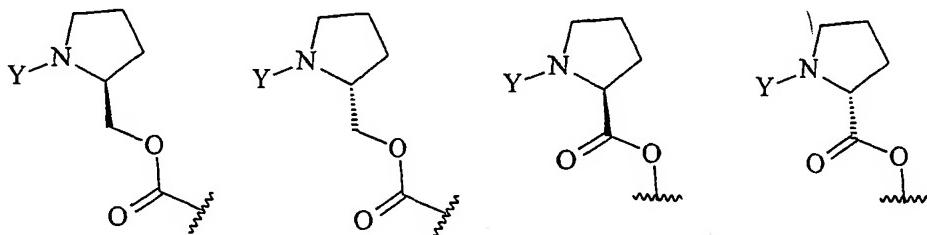
wherein Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetra-methylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzo-furan-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazolinyl, 5-methyl-2-thiazolinyl, 4,5-dimethyl-2-oxazolinyl, 4,5-dimethyl-2-thiazolinyl, 5-phenyl-2-thiazolinyl, 2-thiazolinyl, 4-methyl-5-phenyl-2-thiazolinyl, 5-methyl-4-phenyl-2-thiazolinyl, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-pyridinyl, 6-methoxy-2-pyridinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

12. The compound according to claim 5, wherein X is an N-substituted 2-methylaminoethoxycarbonyl or a N-substituted 2-methylamino-acetoxy, having the following formulas:

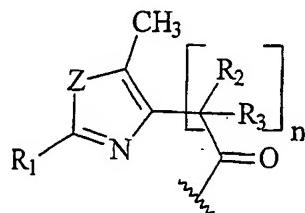


wherein Y is (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (S)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxy, (R)-6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxycarbonyl, (S)-6-hydroxy-2,5,7,8-tetra-methylchroman-2-ylmethoxycarbonyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-carboxy, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxycarbonyl, (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-3-methoxy-carbonyl, 5-chloro-2-pyridyl, 5-methyl-2-pyridyl, 3-chloro-2-pyridyl, 4-methyl-2-pyridyl, 2-pyridyl, 2-benzoxazolyl, 2-benzothiazolyl, 5-amino-2-pyridyl, 5-nitro-2-pyridyl, 2-pyrazinyl, 4-phenyl-2-oxazolinyl, 5-methyl-2-thiazolinyl, 4,5-dimethyl-2-oxazolinyl, 4,5-dimethyl-2-thiazolinyl, 5-phenyl-2-thiazolinyl, 2-thiazolinyl, 4-methyl-5-phenyl-2-thiazolinyl, 5-methyl-4-phenyl-2-thiazolinyl, 2-piperidinyl, 4-phenyl-2-piperidinyl, 6-methyl-2-piperidinyl, 6-methoxy-2-piperidinyl, 2-hydroxybenzoyl, or 2,4-dihydroxybenzoyl.

13. The compound according to claim 5, wherein X is a 1-substituted (R)-pyrrolidine-2-methoxycarbonyl, (S)-pyrrolidine-2-methoxycarbonyl, (R)-pyrrolidine-2-carboxy, or (S)-pyrrolidine-2-carboxy, having the following formulas:

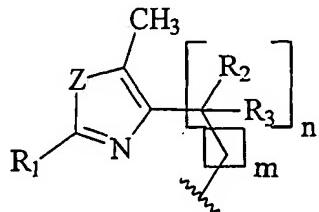


wherein Y is



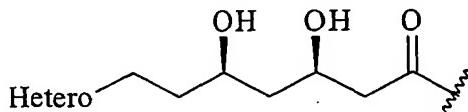
n is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl; or

Y is



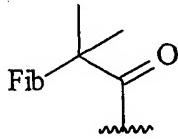
n is 0 or 1; m is 0 or 1; R₂ and R₃ are independently hydrogen or methyl; Z is N, O, or S; and R₁ is aryl, heteroaryl, alkyl, or heteroalkyl or R₁ is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, or 2-pyrazinyl; or

Y is



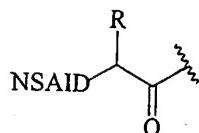
wherein Hetero is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms or Hetero is part of the structure of the statin-family of lipid lowering agents or is 2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1-(1H-pyrrol)yl, or 1,2,3,7,8,8a-hexahydro-1-(2-methylbutanoyl)oxy-3,7-dimethyl-8-naphthalenyl; or

Y is



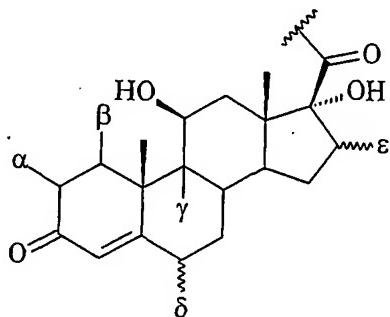
wherein Fib is an aromatic, cyclic, or alicyclic moiety that contains heteroatoms or Fib is part of the fibrate-family of lipid lowering agents, or Fib is 4-(4-chlorobenzoyl)phenoxy, 4-chlorophenoxy, or 3-(2,5-xylyloxy)-1-propyl; or

Y is



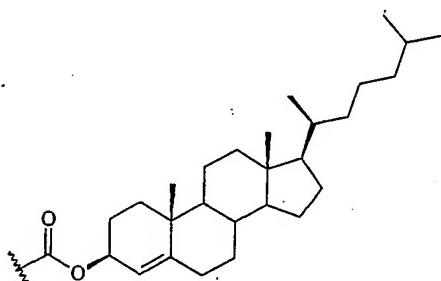
wherein R is hydrogen or methyl, and in which NSAID is an aromatic, alkyl, or cycloalkyl moiety that may contain heteroatoms or NSAID is 4-(2-methyl-1-propyl)phenyl, 2-(2,6-dichloro-1-phenyl)aminophenyl, 6'-methoxy-2'-naphthyl, or 6'-methoxy-2'-naphthylmethyl; or

Y is

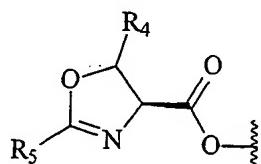


wherein α and β are hydrogen or α and β form a bond, and wherein γ , δ , and ϵ , are independently hydrogen, hydroxy, fluoro, chloro, or methyl; or

Y can be



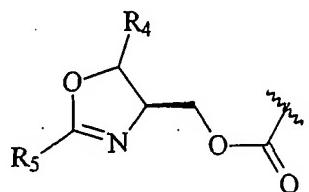
14. The compound according to claim 5, wherein X is



wherein R_4 is hydrogen or methyl and R_5 is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-

isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

15. The compound according to claim 5, wherein X is



wherein R4 is hydrogen or methyl and R5 is phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3-methyl-2-thiophenyl, 5-methyl-2-thiophenyl, 5-methyl-3-isoxazolyl, 2-pyridyl, 4-pyridyl, 2-pyrazinyl, (R)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromanyl, (R)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl, or (S)-5-hydroxy-2,2,4,6,7-pentamethyl-2,3-dihydro-3-benzofuranyl.

16. The compound according to claim 1, wherein A is NH; B is sulfur (S); P and Q are a double bond or hydrogen (H); E is hydrogen (H) and is attached to each of D₁ through D₆; D₁ through D₆ are carbon (C).

17. The compound according to claim 5, wherein A is NH; B is sulfur (S); P and Q are a double bond or hydrogen (H); E is hydrogen (H) and is attached to each of D₁ through D₆; D₁ through D₆ are carbon (C).

18. A composition comprising a carrier and compound according to claims 1-17.

19. The composition according to claim 18, wherein said carrier is a pharmaceutically acceptable carrier.

20. The composition according to claim 18 or claim 19, further comprising additional therapeutic agent.

21. A method of treating diabetes, atherosclerosis, hypercholesterolemia, or hyperlipidemia comprising the administration of a therapeutically effective amount of the composition according to claim 18 claim 19, or claim 20.

22. The method of claim 20, further comprising the administration of additional therapeutic agent.

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(71) Applicant (for all designated States except US): ARYx
THERAPEUTICS [US/US]: Suite 1, 586 Weddell Drive,
Sunnyvale, CA 94089 (US).

(72) Inventors: and

(75) Inventors/Applicants (for US only): DRUZGALA, Pascal [FR/US]; 1512 Mission Boulevard, Santa Rosa, CA 95409 (US). MILNER, Peter, G. [GB/US]; 14690 Manuela Road, Los Altos Hills, CA 94022 (US). PFISTER, Jurg, R. [US/US]; 1500 Oak Avenue, Los Altos, CA 94024 (US).

(74) Agents: EISENSCHENK, Frank, C. et al.; Saliwanchik, Lloyd & Saliwanchik, 2421 N.W. 41st Street, Suite A-1, Gainesville, FL 32606-6669 (US).

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WO 01/81328 A3

(54) Title: THIAZOLIDINEDIONE ANALOGUES AND THEIR USE FOR THE TREATMENT OF DIABETES

(57) **Abstract:** The subject invention provides pharmaceutical compounds useful in the treatment of Type II diabetes. These compounds are advantageous because they are readily metabolized by the metabolic drug detoxification systems. Particularly, thiazolidinedione analogs that have been designed to include esters within the structure of the compounds are provided. This invention is also drawn to methods of treating disorders, such as diabetes, comprising the administration of therapeutically effective compositions comprising compounds that have been designed to be metabolized by serum or intracellular hydrolases and esterases. Pharmaceutical compositions of the ester-containing thiazolidinedione analogs are also taught.

INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 01/13131

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D277/34	C07D417/12	C07D417/14	C07J3/00	A61K31/426
	A61K31/427	A61K31/4439	A61K31/497	A61K31/56	A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 0 528 734 A (ADIR ET COMPAGNIE) 24 February 1993 (1993-02-24) the whole document, particularly example 29 ---	1-22
X	EP 0 549 365 A (SANKYO COMPANY LIMITED) 30 June 1993 (1993-06-30) preparation 23 ---	1-19
X	EP 0 848 004 A (SHIONOGI & CO., LTD.) 17 June 1998 (1998-06-17) page 42, line 25 ---	1-19
X	WO 97 32863 A (TORII PHARMACEUTICAL CO., LTD.) 12 September 1997 (1997-09-12) abstract, and page 4, compound II-b --- -/-	1-22

Further documents are listed in the continuation of box C

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

25 October 2001

Date of mailing of the international search report

08/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax. (+31-70) 340-3016

Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 128:13261 XP002181181 RN 199167-77-6 and 199167-79-8 & JP 09 301963 A (KYORIN PHARMACEUTICAL CO., LTD.) 25 November 1997 (1997-11-25) ---	1-19
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 127:161819 XP002181182 RN 193544-82-0 & JP 09 165371 A (SANKYO CO., LTD.) 24 June 1997 (1997-06-24) ---	1-19
X	KLETZIEN R F ET AL: "Enhancement of adipocyte differentiation by an insulin-sensitizing agent" MOLECULAR PHARMACOLOGY, vol. 41, no. 2, 1 February 1992 (1992-02-01), pages 393-398, XP002081233 the whole document, particularly compound U-90441 ---	1-22
X	UNANGST P C ET AL: "Synthesis and biological evaluation of 5-'3,5-bis(1,1-dimethylethyl)-4-hydroxy phenyl!methylene!oxazoles, -thiazoles, and -imidazoles: Novel dual 5-lipoxygenase and cyclooxygenase inhibitors with antiinflammatory activity" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 2, 1994, pages 322-328, XP002127023 the whole document, particularly page 326, table 4, no. 15e ---	1-20
X	SOHDA T ET AL: "Studies on antidiabetic agents. II. Synthesis of 5-'4-(1-methylcyclohexylmethoxy)-benzyl! thiazolidine-2,4-dione (ADD-3878) and its derivatives" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 10, 1982, pages 3580-3600, XP002042079 the whole document, particularly page 3587, table VI, No. 87 ---	1-22
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INTERNATIONAL SEARCH REPORT

national Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P,X	WO 01 02377 A (GERON CORPORATION ET AL) 11 January 2001 (2001-01-11) the whole document, particularly examples 11, 12, 16 and 19 -----	1-22

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15, 18-22 (all partly)

Present claims 1-15 and 18-22 relate to an extremely large number of possible compounds and their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as recited in claims 16 and 17 (all examples of the application).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/US 01/13131

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